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**Functional Imaging in Primary Headache Syndromes:
Focus on Trigeminal Autonomic Cephalgias**

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**Submitted for the Degree of Doctor of Philosophy
at the
Faculty of Medicine, University of London**

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Declaration

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15 August 2006

Abstract

SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing) and SUNA (Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms) are rare primary headache syndromes, classified with the Trigeminal Autonomic Cephalgias (TACs). Hypothalamic involvement in SUNCT and other TACs has been suggested by functional imaging data and clinically with successful deep brain stimulation.

This thesis studies 52 patients (43 SUNCT, 9 SUNA). It addresses the clinical phenotype of these conditions and response to medications. A functional imaging study explores activation of the posterior hypothalamus in attacks of SUNCT and SUNA, and looks for structural changes in this region on voxel-based morphometry.

The clinical study characterises SUNCT and SUNA in terms of epidemiology of the syndromes, phenotype and clinical characteristics.

A double-blind trial of topiramate in SUNCT showed a 40% response rate, although a similar trial in lamotrigine was less successful. Indomethacin is ineffective in these conditions on single-blind testing. Intravenous lidocaine was effective in all cases. Open-label trials showed the effectiveness of lamotrigine, topiramate and gabapentin.

On functional imaging there was activation bilaterally in the posterior hypothalamus in 5/9 SUNCT patients, and contralaterally in two patients. Two SUNCT patients had ipsilateral negative activation. In SUNA the activation was bilaterally negative. Group analysis showed bilateral activation, although there was no such activation on whole brain analysis. There was no structural change in this region on voxel-based morphometry.

The thesis concludes that there should be revised classification for SUNCT and SUNA, with an increased range of attack duration and frequency, cutaneous triggering of attacks,

and a lack of refractory period. The concept of 'attack load' is introduced. The lack of response to indomethacin, and the response to intravenous lidocaine, are useful in diagnostic and therapeutic measures respectively. Preventive treatments include lamotrigine, gabapentin and topiramate. Hypothalamic activation is discussed in light of the imaging and methodological issues. Finally the role of hypothalamic involvement in SUNCT and SUNA as TACs is considered.

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Publications and Abstracts

Papers

1. Cohen AS, Matharu M, Goadsby PJ. Short-lasting Unilateral Neuralgiform Headache Attacks with Conjunctival injection and Tearing (SUNCT) or Cranial Autonomic Features (SUNA): a prospective clinical study of SUNCT and SUNA. *Brain* 2006; in press.
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2. Cohen AS, Kaube, H. Primary headache disorders and circadian biology: a clinical, imaging and therapy perspective. *Headache Currents* 2005;2:1-7.
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1. (*) Cohen AS, Matharu, M.S., Goadsby, P.J. Revisiting the International Headache Society Criteria for SUNCT and SUNA: a case series of 52 patients. *Cephalalgia* 2005;25:1194.
2. Cohen AS, Matharu, M.S., Goadsby, P.J. Suggested guidelines for treating SUNCT and SUNA. *Cephalalgia* 2005;25:1200.
3. Cohen AS, Matharu, M.S., Goadsby, P.J. ECG abnormalities on verapamil in cluster headache. *Cephalalgia* 2005;25:1200.
4. (**) Cohen AS, Matharu, M.S., Kalisch, R., Friston, K., Goadsby, P.J. Functional MRI in SUNCT shows differential hypothalamic activation with increasing pain. *Cephalalgia* 2004;24:1098-1099.
5. Cohen AS, Matharu, M.S., Goadsby, P.J. Familial paroxysmal hemicrania. *Cephalalgia* 2004;24:1099.

*- was a platform presentation at the International Headache Congress, Kyoto

** - prize winning paper, poster or presentation

Abbreviations

ACC	Anterior Cingulate Cortex
5-HT	5-Hydroxy tryptamine (serotonin)
BOLD	Blood Oxygen-Level Dependent
BNF	British National Formulary
CBZ	Carbamazepine
CH	Cluster Headache
fMRI	functional Magnetic Resonance Imaging
FWHN	Full Width at Half Maximum
GBP	Gabapentin
GLM	General Linear Model
GON	Greater Occipital Nerve
HC	Hemicrania Continua
LTG	Lamotrigine
MRS	Magnetic Resonance Spectroscopy
PAG	Periaqueductal Grey
PET	Positron Emission Tomography
PH	Paroxysmal Hemicrania
rCBF	regional Cerebral Blood Flow
S1	Primary somatosensory cortex
S2	Secondary somatosensory cortex
SCN	Suprachiasmatic nucleus
SPM	Statistical Parametric Mapping
SPECT	Single-photon Emission Computed Tomography
SUNA	Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms
SUNCT	Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing
TAC	Trigeminal Autonomic Cephalgia
TN	Trigeminal Neuralgia

TPM	Topiramate
V₁	First division of the trigeminal nerve
V₂	Second division of the trigeminal nerve
V₃	Third division of the trigeminal nerve
VBM	Voxel Based Morphometry
VPA	Valproate

PART I. INTRODUCTION

Chapter 1

Primary Headache Syndromes and Trigeminal Autonomic Cephalgias

1.1 Primary Headaches

Headache is one of the commonest symptoms for which patients present to doctors in general, and to neurologists more specifically (Linnet et al., 1991; Pascual et al., 1995; Tepper et al., 2004). Primary headache syndromes are those for which there is no underlying structural abnormality or other disorder which is closely temporally related and known to cause headaches (Headache Classification Committee of The International Headache Society, 2004). Common causes for secondary headaches include those attributed to head or neck trauma, cranial or cervical intravascular disorder, non-vascular intracranial disorders such as intracranial hypertension, low cerebrospinal fluid pressure, infection, neoplasm, hypothalamic or pituitary hypo- or hyper-secretion, headaches attributable to a substance or its withdrawal, infection, disorders of homeostasis, disorders of cranium or facial mouth or cranial disorders, and headaches attributable to psychiatric disorder (Headache Classification Committee of The International Headache Society, 2004).

The commonest primary headache syndrome is tension-type headache, which in its episodic form affects 78% of the population, and as chronic tension-type headache affects 3% of the population (Jensen, 2003). Other primary headache syndromes include migraine; the Trigeminal Autonomic Cephalgias (TACs) comprising cluster headache, paroxysmal hemicrania, and SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing); and other primary headache syndromes such as primary stabbing headache, primary cough headache, primary exertional headache, primary headache associated with sexual activity, hypnic headache, primary

thunderclap headache, hemicrania continua, and new daily persistent headache (Headache Classification Committee of The International Headache Society, 2004).

Migraine is a common primary headache syndrome with an overall 1-year prevalence in Europe and North America of 10-12%, and a female:male ratio of 2:1 to 3:1 (Breslau and Rasmussen, 2001). The pain and associated symptoms of migraine attacks carry considerable morbidity. Indeed the World Headache Organisation ranks chronic migraine as one of the leading causes of disability worldwide (World Health Organization, 2001).

Migraine usually manifests as recurrent attacks lasting 4-72 hours, characterised typically by pain of unilateral location, pulsating quality, moderate or severe intensity, and aggravation by routine physical activity; as well as nausea, photophobia or phonophobia. There may be an aura of reversible focal neurological symptoms developing over 5-20 minutes and lasting usually for less than 60 minutes. Chronic migraine occurs on 15 or more days per month for more than 3 months, in the absence of medication overuse (Headache Classification Committee of The International Headache Society, 2004).

1.2 Trigeminal Autonomic Cephalgias (TACs)

Trigeminal Autonomic Cephalgias are relatively rare stereotypical primary headache syndromes which share the following characteristics: they are usually unilateral, the pain is typically peri- or retro-orbital and temporal, and they have associated cranial autonomic symptoms, including conjunctival injection, lacrimation, nasal blockage, rhinorrhoea, eyelid oedema and ptosis. They may be accompanied by agitation. Cluster Headache (CH), Paroxysmal Hemicrania (PH), and SUNCT, are all classified as TACs. Appendix 1 lists the International Headache Society criteria for TACs (Headache Classification Committee of The International Headache Society, 2004).

1.2.1 Cluster headache

Cluster headache (CH) is the commonest of the TACs and therefore the one for which we have the most information. It is a stereotypical primary headache syndrome, characterised by attacks of unilateral excruciating pain usually in the eye, periorbital region and temple, with associated cranial autonomic symptoms. Restlessness and agitation also feature prominently. Attacks can last for 15-180 minutes untreated, and have a frequency of one every other day up to 8 a day (Headache Classification Committee of The International Headache Society, 2004). They can be triggered by alcohol (Bahra et al., 2002), usually in under an hour. This is in contrast to migraine for which alcohol typically has a longer timecourse to triggering an attack.

Attacks usually occur in clusters (bouts) lasting for weeks or months, separated by remissions lasting months or years. Episodic cluster headache (ECH) is defined as bouts of attacks lasting 7 days up to one year, with breaks of one month or more between bouts. Bouts are usually circannual, with a mean bout duration of 8-9 weeks (Bahra et al., 2002). Chronic cluster headache (CCH) is defined as occurring for more than one year with no remission, or with remissions lasting less than one month. CH attacks may also occur with clocklike regularity during the day, and may be precipitated by sleep (Dexter and Weitzman, 1970), usually occurring 90 minutes after the onset of sleep.

With a prevalence of 0.3% in the general population (Sjaastad and Bakkevig, 2003), cluster headache is not as rare as was previously thought. It affects slightly more men than women, with a male: female ratio of 2.5:1 in a recent study (Bahra et al., 2002).

CH is probably the most severe pain known to humans, with most female patients describing each attack as worse than childbirth. Health-related quality of life is significantly impaired in cluster headache sufferers (D'Amico et al., 2002; Ertsey et al., 2004). Even though it is under-recognised and often suboptimally managed in primary care (Geweke, 2002), an early diagnosis and prompt treatment are essential to alleviate the devastating morbidity of these attacks (van Vliet et al., 2003b).

Diagnosis

The diagnosis is usually clear on taking a thorough history. The presence of autonomic symptoms, restlessness, and the length of the attacks usually distinguishes this from migraine, although a proportion of migraine patients may exhibit cranial autonomic features (Barbanti et al., 2002; Dora, 2003), and migraine can coexist with CH (Evans and Bahra, 2004). The differential diagnosis for CH includes the other (TACs), although these differ from CH in that the attack lengths are shorter (Headache Classification Committee of The International Headache Society, 2004), and that PH responds to indomethacin (Antonaci et al., 1998).

The clinical examination is usually entirely normal, although relevant clinical signs may alert the physician to secondary causes of cluster-like headache, including tumors, infections, vascular abnormalities and head trauma (Carter, 2004). These cases may warrant neuroimaging investigations such as CT or MRI, as may cases of new onset CH in older patients, as the mean age of onset of primary CH is 28-37 years, with incidence diminishing with age (Bahra et al., 2002).

Management of CH

The management of CH is threefold; first to avoid the precipitating factors which may trigger an attack during a cluster bout, such as alcohol and afternoon naps; the second is abortive therapy for individual attacks, and the third is preventive medication, which is taken on a daily basis during the cluster bout and long-term in chronic CH, in order to prevent the attacks from occurring.

Abortive therapy

The most effective choice to abort an acute CH attack is serotonin (5-hydroxytryptamine; 5-HT_{1B/D}) agonists, (triptans) in parenteral form. Sumatriptan as 6mg subcutaneous injections has been shown to be efficient in terminating attacks within a few minutes (Diener, 2001; Ekbom et al., 1993; Hardebo, 1993). Sumatriptan nasal spray is also effective, albeit with a slower onset of efficacy (Hardebo and Dahlof, 1998; Schuh-Hofer et al., 2002), is better tolerated than the subcutaneous route (van Vliet et al., 2003a). Oral

zolmitriptan 10mg has been effective in terminating attacks in episodic cluster headache (ECH) but not in chronic cluster headache (CCH) (Bahra et al., 2000). Intranasal zolmitriptan at 5mg and 10mg is effective in patients with ECH or CCH (Cittadini et al., 2005).

The drawbacks of the triptans include limitations of daily usage. Current practice is to limit sumatriptan usage to 2 subcutaneous injections or 3 nasal sprays a day, in order to prevent tachyphylaxis and rebound. At this dosage, there was no tachyphylaxis even in long-term use (Ekbom et al., 1992). Triptans are also contraindicated in patients for whom there is a vascular risk such as ischaemic heart disease.

The other first-choice abortive treatment for acute CH attacks is the inhalation of high-dose, high-flow oxygen at 100% for 15 minutes at the start of the attack, which is safe and effective in aborting a CH attack (Kudrow, 1981), and this has been confirmed in a small controlled study (Fogan, 1985). However good controlled evidence in a large-scale trial for the effectiveness of oxygen therapy in acute cluster attacks is lacking. Hyperbaric oxygen has been shown to be effective, but no more so than hyperbaric air in a recent study (Nilsson Remahl et al., 2002).

Other abortive therapies include topical agents such as intranasal lidocaine which has been reported as successful (Hardebo and Elner, 1987; Kittrelle et al., 1985). A placebo-controlled trial of intranasal capsaicin showed reduced severity of attacks, especially in ECH (Marks et al., 1993), but is used less often in clinical practice because of local side effects.

Preventive treatment

The importance of an effective preventive treatment is paramount. When optimally managed, the patient's attacks can often be suppressed entirely on prophylactic therapy for the duration of the bout in ECH, or longer-term in CCH, with a minimal side-effect profile and without the need for acute abortive agents.

Short-term prophylaxis

Many of the preventive drugs for longer-term prophylaxis require several weeks of dose escalation, thus making them unsuitable for patients with shorter bouts. Short-term preventives may be appropriate in these cases, or in patients whose headaches are uncontrolled and who require rapid control of their attack frequency.

Corticosteroids are very effective and fast-acting in the prevention of CH attacks (Couch and Ziegler, 1978; Kudrow, 1980). However the CH attacks usually recur shortly after the steroid treatment has been stopped. Steroids may therefore be used in conjunction with other preventives during their phase of dose escalation, until they are effective. There has been one open-label study documenting the effectiveness of intravenous methylprednisolone followed by a reducing dose of oral steroids in ECH (Mir et al., 2003).

Until recently, triptans were thought not to be useful in prophylaxis of CH due to their short half-lives. However longer acting agents such as naratriptan (Mulder and Spierings, 2002), eletriptan (Zebenholzer et al., 2004) and frovatriptan (Siow et al., 2004) have been used as add-on therapy to verapamil in the short-term management of CH.

Longer-term prophylaxis

The first choice is verapamil, which has been shown to be effective in episodic and chronic cluster headache (Bussone et al., 1990; Gabai and Spierings, 1989; Leone et al., 2000a), and to cause fewer side effects and have a shorter latency period when compared to lithium (Bussone et al., 1990). Two randomised controlled trials used verapamil at a dose of 360 mg daily (Bussone et al., 1990; Leone et al., 2000a), and an open trial used an increasing regime of doses up to 1200mg daily (Gabai and Spierings, 1989). Side effects of verapamil were reported as constipation, vertigo, nausea, asthenia, ankle swelling, bradycardia, and stomach cramps. Interestingly the patients who had to discontinue the drug because of side effects were at the lower dose (240 mg daily).

Clinical experience has shown that higher doses of verapamil than those used in cardiological indications are needed in cluster headache (Olesen, 1999). Excessive concentrations of verapamil have been shown to cause atrio-ventricular block (Frishman et al., 1982; Seipel and Breithardt, 1982). The incidence of arrhythmias was reported at 18% in a recent series, with bradycardia in 37% of patients (Cohen et al., 2005).

The second choice for preventive treatment is lithium, which has been proven effective in both ECH and CCH (Bussone et al., 1990; Ekbom, 1981; Steiner et al., 1997b). Renal and thyroid functions should be checked before and during treatment, and the serum levels of lithium determined at regular intervals (Ekbom, 1995).

Methysergide has been used in cluster headache since the 1950s (Ekbom, 1995). It is an ideal choice in patients with short bouts of up to 4-5 months. Prolonged treatment has been associated with fibrotic reactions (pleural, pericardial, retroperitoneal and pulmonary), but these are rare (Graham et al., 1966), and can be avoided by using methysergide for less than six months at a time.

Another treatment which is emerging as being useful in CH is topiramate at doses of 75-200mg daily (Forderreuther et al., 2002) in ECH and CCH (Lainez et al., 2003). However there is some conflicting evidence (Leone et al., 2003a), and care must be taken to avoid potential side-effects which include dyspepsia, distal limb paraesthesiae, ataxia, dizziness, weight loss in 10% of patients, exacerbation of renal stones in those predisposed to them, and cognitive impairment ranging from mild memory slowing to frank psychosis in a small number of patients. However, if side effects are minimal or tolerable, topiramate remains a valuable and feasible treatment option in cluster headache. One approach is to start with a dose of 12.5mg daily and increase every week by 12.5 or 25mg to a maximum daily dose of 200-400mg. Both the therapeutic and unwanted effects may not occur in a strictly dose-dependent fashion.

Other anti-epileptic therapies such as sodium valproate (El Amrani et al., 2002b; Gallagher et al., 2002) and gabapentin (Leandri et al., 2001) have been used in CH but

without good controlled evidence. Given the diurnal nature of many CH attacks, melatonin has been tried in order to combat the reduced nocturnal melatonin in CH patients. A double-blind study of melatonin treatment significantly reduced headache frequency in episodic, but interestingly not chronic, CH sufferers (Leone et al., 1996; Pringsheim et al., 2002), although an open-label trial of melatonin as add-on therapy in two chronic CH patients was successful (Peres and Rozen, 2001).

As for the use of botulinum toxin in CH, there have been positive and negative case reports, but no randomised controlled trials have been done yet (Sycha et al., 2004).

Neuromodulatory Procedures

There is a subset of patients with CH which appears to be refractory to current medical treatment options, or for whom side effects and contraindications preclude the use of effective therapeutics. In these cases, and also in patients who require rapid control of attack frequency, a subcutaneous injection of lidocaine and depomedrone in the region of the Greater Occipital Nerve (GON) is an option as transitional therapy to be started at the same time as preventive medications (Peres et al., 2002). An acute local anaesthetic injection into the region of the GON has been shown to abort a CH attack (Anthony, 1987). A placebo-controlled study of betamethasone could suppress attacks in more than 80% of CH patients, with the effect maintained for at least 4 weeks in the majority of them (Ambrosini et al., 2005). This blockade could interfere in the trigeminal activity in cluster headache and potentially interrupt the trigeminal autonomic reflex pathway (Goadsby et al., 1999). Being a non-systemic treatment, the side-effects are rare and limited to mild paraesthesiae and a small area of hair loss at the site of injection (Shields et al., 2004).

Surgery

Surgery is a last-resort measure for patients with CH which is resistant to all other treatments. Procedures such as radiofrequency blockade of the sphenopalatine ganglion in a series including 10 patients with CH (Sanders and Zuurmond, 1997), and percutaneous radiofrequency rhizotomy in seven patients (Taha and Tew, 1995), have had variable

effects ranging from no relief to pain free at 20 years' followup. Trigeminal nerve section has also had variable results, ranging in two series from no effect to pain free at 19 years (Jarrar et al., 2003; Kirkpatrick et al., 1993). Occasionally complete trigeminal anaesthesia is achieved, with subsequent risk of corneal injury (Jarrar et al., 2003; Kirkpatrick et al., 1993). Gamma knife radiosurgery has also been used in CH (Ford et al., 1998), although a prospective study found that the high morbidity and low efficacy precluded its use in mainstream CH treatment (Donnet et al., 2005). Destructive surgery in order to block trigeminal sensory or autonomic pathways should only be considered in patients with strictly unilateral attacks, as those whose attacks alternate sides may find an upsurge of attacks on the side contralateral to surgery (Jarrar et al., 2003). In one devastating case the CH attacks persisted even after complete destruction of the trigeminal sensory pathway (Matharu and Goadsby, 2002a). This provides further evidence that CH is a central nervous system disorder as opposed to being a peripheral nerve or vascular headache.

Functional imaging data has suggested the hypothalamus to be the origin for cluster headache (reviewed (Cohen and Goadsby, 2004)). There have been recent successes with abolition of attacks by the insertion of deep brain stimulators to the posterior hypothalamus in CH (Franzini et al., 2003; Leone et al., 2003b; Schoenen et al., 2005), and this clearly may prove a viable option in the future, for patients with otherwise refractory CCH. A less invasive procedure involves inserting a stimulator subcutaneously in the region of the GON, as it is known that pain afferents from the trigeminal and occipital nerves converge at the trigeminocervical complex (Bartsch and Goadsby, 2003b), and in animal models stimulation of the greater occipital nerve alters metabolic activity in the trigeminal nucleus caudalis and cervical dorsal horn (Goadsby et al., 1997), and increases excitability from afferents from the first trigeminal nerve (Bartsch and Goadsby, 2002). Occipital nerve stimulation has been reported as effective in patients with migraine (Matharu et al., 2004a), occipital neuralgia (Kapural et al., 2005), cluster headache (Dodick et al., 2003; Peres et al., 2002) and in one case each of CH and hemicrania continua (Schwedt et al., 2006), although with persistence of autonomic

symptoms in the latter two cases, indicating a central cause for the autonomic symptoms which was not altered by modulation of the trigeminocervical pain system.

1.2.2 Paroxysmal Hemicrania

Paroxysmal Hemicrania (PH) is a severe, strictly unilateral headache centred on the orbital, supra-orbital or temporal regions, lasting two to 30 minutes and occurring with an attack frequency above five daily for more than half of the time, although periods with lower frequency may occur. The attacks are associated with one or more of the following cranial autonomic features: conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, eyelid oedema, forehead and facial sweating, miosis, and ptosis. A complete response to indomethacin is a prerequisite for diagnosis by the classification criteria of the International Headache Society (Headache Classification Committee of The International Headache Society, 2004).

PH was first described by Sjaastad and Dale in 1974 (Sjaastad and Dale, 1974) when they reported a case they rather aptly named "a new treatable headache entity". They subsequently coined the term "chronic paroxysmal hemicrania" to describe these patients (Sjaastad and Dale, 1976). Later, a remitting form of the disease was recognized and termed "episodic paroxysmal hemicrania" (Kudrow et al., 1987). The release of the second edition of the IHS Classification resulted in the introduction of the umbrella term "paroxysmal hemicrania" that is recognized to have both an episodic and a chronic form (Headache Classification Committee of The International Headache Society, 2004). The episodic form occurs during a period that lasts seven days to one year and is separated by pain-free periods that last one month or more. The chronic form has attacks that occur for more than one year without remission or with remissions lasting less than one month.

A requirement of PH is that it is absolutely responsive to indomethacin, whereas CH and SUNCT are not (Antonaci et al., 2003; Antonaci et al., 1998; Cohen et al., 2005c; Matharu et al., 2004b). There are some reports of CH responsive to indomethacin (Buzzi and Formisano, 2003; Geaney, 1983; Klimek, 1984), although these are rare and not

placebo controlled. Hemicrania continua, although not a TAC, is another primary headache syndrome with some cranial autonomic features which responds absolutely to indomethacin (Headache Classification Committee of The International Headache Society, 2004).

Side-effects of indomethacin include gastric irritation in 23% of patients (Pareja et al., 2001), which has necessitated the withdrawal of indomethacin in PH, and using alternatives such as cyclo-oxygenase 2 (COX-2) inhibitors (rofecoxib, valdecoxib and celecoxib) (Lisotto et al., 2003; Mathew et al., 2000; Siow, 2004), and calcium channel blockers (Coria et al., 1992). Topiramate is a neuromodulator which is effective in the prevention of migraine (Brandes et al., 2004; Diener et al., 2004; Silberstein et al., 2004), and probably effective in cluster headache (Forderreuther et al., 2002; Lainez et al., 2003; Mathew et al., 2002; Wheeler and Carrazana, 1999), and SUNCT (Cohen et al., 2005c; Matharu et al., 2002; Matharu et al., 2004b; Rossi et al., 2003). There is a case report of the effectiveness of topiramate in paroxysmal hemicrania-tic syndrome (Boes et al., 2003), and one in post traumatic PH (Cohen and Goadsby 2006, Paroxysmal hemicrania responding to topiramate; accepted for publication in Journal of Neurology Neurosurgery and Psychiatry, Appendix 2).

1.3 SUNCT and SUNA

SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing) is a rare primary headache syndrome first described in 1978 (Sjaastad, 1978). The syndrome has been described more fully over subsequent years (Pareja and Sjaastad, 1997; Sjaastad et al., 1989), although in small series. It has been suggested that it be grouped together with cluster headache and paroxysmal hemicrania as a Trigeminal Autonomic Cephalalgia (TAC) (Goadsby and Lipton, 1997) based on the now classical clinical combination of head pain and activation of cranial autonomic efferents (May and Goadsby, 1999). The syndrome was included in the second edition of the International Headache Classification (Headache Classification Committee of The

International Headache Society, 2004), as was the syndrome of SUNA: Short-lasting Unilateral Neuralgiform Headache attacks with cranial Autonomic symptoms.

SUNCT is defined by the International Headache Society as being characterised by unilateral orbital or temporal pain which is stabbing or throbbing in quality and of moderate severity. There should be at least 20 attacks, lasting for 5-240 seconds and ipsilateral conjunctival injection and lacrimation should be present (Headache Classification Committee of The International Headache Society, 2004). In recognition of the possibility that all patients with generically the same condition might not have both conjunctival injection and tearing, the classification committee considered that SUNCT syndrome may be a subset of SUNA, Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic features. In SUNA there may be cranial autonomic symptoms other than conjunctival injection and lacrimation, or indeed only one of those symptoms may be present. Since publication of that classification there has been little by way of case reports of SUNA (Volcy et al., 2005).

A comprehensive review of 50 cases of SUNCT from the worldwide literature was published in 2003 (Matharu et al., 2003a), and there have been further case reports since then (Black et al., 2005; Calvo et al., 2004; Cohen et al., 2004; Malik et al., 2002; Matharu et al., 2004b; Matharu et al., 2003c; Prakash and Lo, 2004; Ramirez-Moreno et al., 2004; Rossi et al., 2003; Sekhara et al., 2005; Vikelis et al., 2005). The typical age of onset is between 35 and 65 (68% of primary SUNCT cases) (Matharu et al., 2003a), but ranges from 5 (Sekhara et al., 2005) to 88 years (Vikelis et al., 2005). SUNCT appears to have a male predominance, with one review of 15 men and 4 women stating the male:female ratio of 3.75:1 (Pareja and Sjaastad, 1997), and a subsequent review of 28 men and 22 women stating the male:female ratio at 1.3:1 (Matharu et al., 2003a). The trend towards increasing female preponderance over time, and the emergence of new cases at the extremes of age of onset, reflect an increasing recognition of these conditions in the general population.

SUNCT is usually a primary headache syndrome. However there are a number of cases which are secondary to intracranial lesions, typically either in the posterior fossa or in the pituitary gland. Case reports of SUNCT secondary to a posterior fossa abnormality include the following: ipsilateral cerebellopontine arteriovenous malformations in two patients (Bussone et al., 1991; Morales et al., 1994), a brainstem cavernous haemangioma (De Benedittis, 1996), a posterior fossa lesion associated with HIV/AIDS (Goadsby and Lipton, 1997), severe basilar impression causing pontomedullary compression in a patient with osteogenesis imperfecta (ter Berg and Goadsby, 2001), craniostosis resulting in a foreshortened posterior fossa (Moris et al., 2001), ischaemic brainstem infarction (Penart et al., 2001), a pilocytic astrocytoma expanding to the trigeminal root entry zone (Blattler et al., 2003) and a plaque of multiple sclerosis in the anterior pons, ipsilateral cerebral peduncle, and medulla (Vilisaar and Constantinescu, 2006). There has also been a recent report of SUNCT secondary to intraorbital metastatic bronchial carcinoid, which although not in the posterior fossa, would meet criteria proposed by Trucco et al to identify causal links in secondary SUNCT (Trucco et al., 2004).

As for pituitary lesions, a patient with a pituitary macroadenoma had reported symptoms of SUNCT which were labeled as trigeminal neuralgia (Ferrari et al., 1988). SUNCT has been described in patients both with microprolactinomas (Levy et al., 2003) and macroprolactinomas (Massiou et al., 2002; Matharu et al., 2003c), with attacks occurring on the side ipsilateral to the side of the tumour, suggesting a role for a direct or mechanical mode of action in macroadenomas, but this would not account satisfactorily for microadenomas. It has therefore been suggested that the attacks were predominantly neurohormonally mediated rather than by the size or invasiveness of the tumour (Matharu et al., 2003c). It is also interesting to note that headache symptoms can precede pituitary symptoms by 3-10 years (Ferrari et al., 1988; Massiou et al., 2002).

A difficulty in defining the clinical characteristics of a rare syndrome is to obtain sufficient experience in one place and case histories to make comparisons and see common themes. This has not been hitherto possible with SUNCT/SUNA. This thesis presents a case series of 52 patients with SUNCT or SUNA, which is a substantial

enough cohort to compare and contrast the clinical presentation. The clinical and epidemiologic characteristics of a large clinic-based population of persons with SUNCT and SUNA were prospectively studied. This study addresses the clinical characteristics of the syndrome and the management strategies used. The phenotype of the attacks is reported in more detail than has been previously described. The work was initially reported at the 12th Congress of the International Headache Society (Cohen et al., 2005b).

1.4 SUNCT and Trigeminal Neuralgia

The diagnosis of SUNCT is often confused with trigeminal neuralgia (TN), which is categorised by the International Headache Society classification as one of the cranial Neuralgias and central causes of facial pain (Headache Classification Committee of The International Headache Society, 2004). It is a unilateral disorder affecting 4.3 per 100 000 people annually (Wilkins, 2002). Attacks are characterised by brief electric-shock-like pains, abrupt in onset and termination, in one or more distributions of the trigeminal nerve (Headache Classification Committee of The International Headache Society, 2004), usually the maxillary (V₂) or mandibular (V₃) divisions, and rarely in the ophthalmic division (V₁). It can be precipitated by trivial stimuli such as washing, shaving, smoking, talking and brushing the teeth, although attacks can occur spontaneously. The pains usually remit for variable periods.

Neurovascular compression in the root entry zone of the trigeminal nerve in the cerebellopontine angle cistern of the trigeminal nerve is widely believed to be the essential mechanism for the pathogenesis of TN (Dandy, 1934; Gardner and Miklos, 1959; Jannetta, 1980), with 10% (Adams et al., 1982) to 100% of patients (Jannetta, 1985) having operatively confirmed vascular compression. Magnetic resonance (MR) imaging (Majoie et al., 1997) and magnetic resonance angiographic techniques (Boecker-Schwarz et al., 1998; Meaney et al., 1995) are useful to detect neurovascular compression in TN. Microvascular decompression (the Jannetta procedure) is a useful method to treat trigeminal neuralgia (Barker et al., 1996), as are gamma-knife radiosurgery and glycerol rhizotomy (Henson et al., 2005). From a medical treatment

perspective, the gold standard is treatment with carbamazepine (Campbell, 1966; Killian and Fromm, 1968; Nicol, 1969; Rockliff and Davis, 1966). Other neuromodulators such as gabapentin (Serpell, 2002), and lamotrigine as an add-on therapy (Zakrzewska et al., 1997), and topiramate (Gilron et al., 2001) have shown benefit, as have the muscle relaxants baclofen (Fromm et al., 1984) and tizanidine (Fromm et al., 1993), and the anti-arrhythmic tocainamide (Backonja, 2000; Lindstrom and Lindblom, 1987).

Given the short, stabbing nature of the attacks, the cutaneous triggering, and the association of cranial autonomic symptoms with V_1 pain, the differentiation between TN and SUNCT has often been difficult (Sesso, 2001), especially in the elderly (Cohen et al., 2004). SUNCT and TN were thought to coexist as two separate headache entities in a patient with neurovascular compression at the ipsilateral trigeminal root entry zone (Zidverc-Trajkovic et al., 2005). Indeed SUNCT has been reported in a case with ipsilateral neurovascular compression, although it is not clear in this case whether surgical intervention would have relieved the symptoms (Koseoglu et al., 2005).

SUNCT has previously been thought to be a form of transformed TN based on the shared phenomenology in a case report (Bouhassira et al., 1994). TN with lacrimation has been reported in six cases, and in the same series in 16 cases without lacrimation (Benoliel and Sharav, 1998). It is also discussed in older texts from as early as 1888 (Collier, 1922; Gowers, 1888; Kinnier Wilson, 1940). A series of 19 patients with V_1 TN suggested that although 8 of them had autonomic phenomena, these were likely to be relatively 'mild' compared to autonomic symptoms in SUNCT (Sjaastad et al., 1997).

Cranial autonomic symptoms such as conjunctival injection and lacrimation are thought to result, in part, from activation of the trigeminal-autonomic reflex (May and Goadsby, 1999), and are recognised in other forms of head pain, including experimental head pain with capsaicin injection (May et al., 1999) and other headache syndromes such as migraine (Barbanti et al., 2002; Benoliel and Sharav, 1998). In fact, some degree of cranial autonomic symptomatology is a normal physiologic response to cranial nociceptive input (Frese et al., 2003; May et al., 2001). The distinction between TACs

(such as SUNCT) and other headache syndromes (such as TN) appears to be the degree of cranial autonomic activation (Goadsby et al., 2001), as was borne out in an objective assessment of autonomic signs during attacks of triggered V_1 TN, where mild lacrimation was observed, even in relatively long attacks, in clear contradiction with SUNCT where conjunctival injection and lacrimation are dramatic on the ipsilateral side (Pareja et al., 2002). It has been suggested that the cranial autonomic symptoms may be prominent in TACs due to a central disinhibition of the trigeminal-autonomic reflex by the hypothalamus (Benjamin et al., 2004).

1.5 Treatments for SUNCT

SUNCT has until recently been considered refractory to treatment. However it has now been shown in open-label trials that neuromodulatory treatments such as lamotrigine (D'Andrea et al., 1999a; D'Andrea et al., 2001; Gutierrez-Garcia, 2002; Leone et al., 2000b; Malik et al., 2002), carbamazepine (Matharu et al., 2003a; Matharu et al., 2004b), topiramate (Matharu et al., 2002; Matharu et al., 2004b; Rossi et al., 2003), and gabapentin (Graff-Radford, 2000; Hunt et al., 2002; Porta-Etessam et al., 2002) have been successful in the preventive treatment of some cases of SUNCT.

Drug therapies

Several categories of drugs used in headache and other pain syndromes have been tried in SUNCT, a large number of which have been reviewed extensively (Matharu et al., 2003a). Most of them have been reported to be ineffectual, and until recently SUNCT was thought to be highly refractory to treatment.

Serotonergic agonists and antagonists

Sumatriptan, either in oral form (100-300mg daily), or subcutaneously (6mg), has been reported with little or no response in SUNCT (Matharu et al., 2003a). Oral or intravenous dihydroergotamine was also ineffectual. Methysergide and pizotifen have also had no reported effect (Goadsby and Lipton, 1997; Matharu et al., 2004b; Pareja et al., 1995).

Selective serotonin reuptake inhibitors (SSRIs) have been used in SUNCT, including sertraline (100mg/day) (Koseoglu et al., 2005) and fluoxetine (20mg/day) (Matharu et al., 2004b), with no effect.

Oxygen

High-dose high-flow oxygen has been used to good effect in cluster headache (Fogan, 1985; Kudrow, 1981), but has had little or no effect in SUNCT (Matharu et al., 2003a; Matharu et al., 2004b). It is arguable that any benefit seen in SUNCT patients may be due to the spontaneous resolution of each attack over seconds to a few minutes, rather than any beneficial therapeutic effect.

Indomethacin, non-steroidal anti-inflammatory drugs and cyclo-oxygenase inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, piroxicam, naproxen, ketoprofen, aspirin and mefenamic acid, are ineffective in the treatment of SUNCT and SUNA (Matharu et al., 2003a; Matharu et al., 2004b; Rossi et al., 2003; Volcy et al., 2005). Oral indomethacin in doses up to 300mg a day has also been found to be mainly ineffective (Gardella et al., 2001; Hunt et al., 2002; Koseoglu et al., 2005; Matharu et al., 2004b; Narbone et al., 2005; Prakash and Lo, 2004; Rossi et al., 2003; Volcy et al., 2005).

Lidocaine

Intravenous lidocaine has been reported previously in 4 patients with SUNCT, providing them with pain free times of up to 12 hours (Matharu et al., 2004b), and in a further case with pain relief for an unknown time (Shiiba et al., 2005).

Preventive Medications

Lamotrigine

Recently, lamotrigine given in an open-label manner at doses up to 300mg daily was reported as highly efficacious in 10 patients (D'Andrea et al., 1999a; D'Andrea et al., 2001; Gutierrez-Garcia, 2002; Leone et al., 2000b; Malik et al., 2002), although it was ineffective in 4 patients (Black and Dodick, 2002; Matharu et al., 2004b; Sprenger et al.,

2005), and ineffective at 400mg daily in a patient with SUNCT related to trigeminal nerve compression (Koseoglu et al., 2005).

Problems with lamotrigine include a skin reaction which may progress to Stevens-Johnson syndrome, and this necessitated the cessation of lamotrigine in at least 1 patient in the literature (Rossi et al., 2003).

Topiramate

Topiramate has been reported to be effective in 5 patients at doses up to 300mg daily (Matharu et al., 2002; Matharu et al., 2004b; Rossi et al., 2003), and ineffective in three patients (Black and Dodick, 2002; Koseoglu et al., 2005). Problems with topiramate include side effects, which sometimes necessitated the cessation of the drug. Two patients reported mild hypersomnolence at doses of 75 and 300mg a day respectively, but as they were rendered pain free and the headaches recurred on reducing the dose, they maintained the topiramate treatment (Matharu et al., 2004b; Rossi et al., 2003).

Carbamazepine

Carbamazepine has been a mainstay of treatment in trigeminal neuralgia (Backonja and Serra, 2004), and has also been reported as having a good or partial effect in SUNCT at doses up to 900mg a day (Matharu et al., 2003a; Matharu et al., 2004b), especially when used in combination with naloxone, verapamil and lithium (Sabatowski et al., 2001); prednisolone (Calvo et al., 2004; Gardella et al., 2001; Montes et al., 2001), topiramate (Matharu et al., 2004b), and indomethacin (Prakash and Lo, 2004). However there are some reports of carbamazepine having no effect at doses of 100-1200mg a day (Cohen et al., 2004; Koseoglu et al., 2005; Rossi et al., 2003), and only a mild effect at 1600mg a day (Gantenbein and Goadsby, 2005).

Gabapentin

SUNCT has been shown to respond to gabapentin, with complete suppression of attacks in three of nine patients treated with 800 to 2700 mg daily (Graff-Radford, 2000; Hunt et al., 2002; Porta-Etessam et al., 2002), and minimally effective in 1 patient with SUNA at

an unknown dose (Volcy et al., 2005). However it has been reported as completely ineffective in 9 patients (Koseoglu et al., 2005; Malik et al., 2002; Matharu et al., 2003a; Matharu et al., 2004b), although in 1 patient this was SUNCT secondary to compression of the trigeminal nerve (Koseoglu et al., 2005).

Valproate

Valproate, which is used commonly in migraine (Hering and Steiner, 1994; Jensen et al., 1994), has been ineffective in doses up to 2000 mg a day in 8 patients with SUNCT, was partially effective in one, and transiently had a good effect when combined with nortriptyline and prednisolone in another patient (Matharu et al., 2004b; Pareja et al., 1995; Sesso, 2001). It was ineffective in a patient with SUNA at 15mg/kg/day (375mg/day) (Volcy et al., 2005).

Verapamil and Lithium

Verapamil at high doses (up to 960mg/day), and lithium (to a therapeutic range of 0.8-1.1 µmol/l) are usually used in cluster headache (Bussone et al., 1990; Ekbom, 1981; Leone et al., 2000a), and have had little or no reported effect in SUNCT (Gardella et al., 2001; Matharu et al., 2003a; Rossi et al., 2003), or verapamil has made the attacks worse (Jimenez-Huete et al., 2002; May et al., 1999b), except in one recent case where verapamil at doses of 480-960mg a day abolished attacks in a patient with SUNCT and an ischaemic lesion in the posterior fossa (Narbone et al., 2005). Lithium and verapamil are both known to accumulate in the hypothalamus (Bussone, 2003; Dodick et al., 2003), which plays an important role in the generation of both CH and SUNCT attacks, so it would be intuitive that they may both have some beneficial effect in SUNCT.

Corticosteroids

Corticosteroids, particularly prednisolone, are used in the treatment of cluster headache (Antonaci et al., 2005; Couch and Ziegler, 1978; Kudrow, 1980). There have been some benefits reported in SUNCT with steroid monotherapy (Matharu et al., 2003a), although there is another report showing no benefit of 60mg prednisolone for 1 month (Rossi et al.,

2003). Steroids have also been used in combination with carbamazepine at doses of 40-60mg/day (Calvo et al., 2004; Gardella et al., 2001; Montes et al., 2001).

Adrenoreceptor blockers

Beta-blockers such as propranolol, and alpha-blockers such as clonidine, have been shown to be ineffective in SUNCT (Matharu et al., 2003a).

Amitriptyline and tricyclic antidepressants

Amitriptyline and other tricyclic antidepressants are commonly used in the treatment of migraine (Couch et al., 1976; Punay and Couch, 2003; Ziegler et al., 1987), neuropathic pain (McQuay et al., 1996; Sindrup and Jensen, 1999) and atypical facial pain (Lascelles, 1966), but there are no randomised controlled trials of amitriptyline in trigeminal neuralgia or SUNCT.

Phenytoin

Phenytoin has been tried in 10 patients and was reported to be ineffective in all except one in whom a possible slight improvement was noted (Malik et al., 2002; Pareja et al., 1995). It has been used in combination with carbamazepine, which had no beneficial effect but caused ataxia (Matharu et al., 2004b).

Other anticonvulsants

Other drugs used with little or no effect include oxcarbazepine (2400mg/day (Sprenger et al., 2005)) (1800mg/day in the patient with SUNCT associated with compression of the trigeminal nerve) (Koseoglu et al., 2005), baclofen, both alone and in combination with carbamazepine (Calvo et al., 2004), and clonazepam (Matharu et al., 2004b).

Analgesics

Simple analgesics (paracetamol, aspirin) opiates (morphine, tramadol, buprenorphine, dihydrocodeine), and combination analgesics (paracetamol/codeine, hydrocodone/acetaminophen), have all been reported as ineffective (Malik et al., 2002; Matharu et al., 2003a; Matharu et al., 2004b; Putzki et al., 2005).

Surgery

Several surgical approaches have been attempted for the treatment of SUNCT syndrome. These take the form either of local blockades, invasive procedures involving the trigeminal nerve, and neuromodulatory procedures using superficial nerve and deep brain stimulation.

Local Blockades

Local blockades of pericranial nerves with anaesthetics, alcohol, phenol, or opioids, have generally been reported as ineffectual. Supraorbital blockades using lidocaine, bupivacaine or alcohol, were ineffective in suppressing spontaneous attacks in nine patients, but made triggering of attacks more difficult by touching the anaesthetised area (Hannerz and Linderöth, 2002; Pareja et al., 1995). Infraorbital blockades were ineffective in 8 of nine patients (Hannerz and Linderöth, 2002), and lidocaine blockades of lacrimal nerve, orbicularis oculi muscles, and the retrobulbar region also had no effect, as did a stellate ganglion block with bupivacaine (Pareja et al., 1995). A pterygopalatine ganglion blockade with phenol produced a variable effect in one patient (Hannerz and Linderöth, 2002), and one had a partial response with opioid blockade of the superior cervical ganglion (Sabatowski et al., 2001).

Invasive surgical procedures involving the trigeminal nerve

Two patients have been treated with the Jannetta procedure (microvascular decompression of the trigeminal nerve) with good effect (Gardella et al., 2001; Lenaerts, 1997), although in one patient it made the symptoms worse (Matharu et al., 2004b), and in 2 further patients it was unhelpful, as were glycerol rhizotomy and γ knife radiosurgery, and in fact the patients suffered post surgical side effects which were anaesthesia dolorosa, unilateral deafness, chronic vertigo and disequilibrium (Black and Dodick, 2002). One patient underwent a right trigeminal radiofrequency thermocoagulation, after which she was pain free for 3 years, but with marked hypoanaesthesia over the second and third trigeminal distributions on that side (Matharu et al., 2004b). Some authorities recommend that trigeminal surgery be considered only as a last resort, and then with extreme caution, given its uncertain outcomes and the

potential for debilitating side effects. Others suggest that it has no place in current therapy.

Hypothalamic deep brain stimulation

Functional imaging work has shown that activation of the posterior hypothalamus is linked to attacks of cluster headache (May et al., 1998a; Sprenger et al., 2004), and SUNCT (Cohen et al., 2004a; May et al., 1999b; Sprenger et al., 2005). Sixteen patients with intractable chronic cluster headache and one patient with intractable SUNCT have undergone deep brain electrical stimulation to the posterior hypothalamus, with good results (Leone et al., 2004a; Leone, 2004). In another series of six patients, 2 were painfree with a third patient with much reduced frequency of attacks. However the side effect of diplopia limited the increase of the voltage, and one patient died of an intracerebral haemorrhage (Schoenen et al., 2005). Therefore the referral of patients for these procedures is done with great caution, and currently is reserved for those patients who are refractory to all other types of treatment.

Greater occipital nerve injections

Two patients with SUNCT and 6 patients with PH underwent lidocaine blockades of the greater occipital nerve with no benefit (Antonaci et al., 1997; Pareja et al., 1995).

Other non-pharmacological procedures

One patient tried a transcutaneous electrical nerve stimulation (TENS) machine, acupuncture, and a maxillary bite appliance, all with no effect (Matharu et al., 2004b).

Chapter 2

Functional imaging in primary headaches

2.1 Introduction

Primary headache disorders, such as migraine and cluster headache, have until recently been described as vascular headaches. However there is now considerable imaging and clinical evidence to suggest that they are primarily driven from the brain (Goadsby, 2002b; Goadsby et al., 2002). Early functional imaging work using positron emission tomography (PET) has shed light on the genesis of these syndromes, documenting activation in the midbrain and pons in migraine, and in the posterior hypothalamic grey in cluster headache and other trigeminal autonomic cephalgias. PET has also been used to show both hypothalamic and brainstem activation in hemicrania continua, a syndrome which shares features both with migraine and the trigeminal autonomic cephalgias.

These areas are involved not simply as a response to first division nociceptive pain impulses but specifically in each syndrome, probably in a permissive or dysfunctional role. Further studies using functional magnetic resonance imaging techniques, voxel-based morphometry and magnetic resonance spectroscopy, all add evidence that these primary headache syndromes are primarily brain disorders.

2.2 Techniques

The concept of ‘intrinsic mechanisms’ responsible for coupling neural activity with cerebral blood flow was introduced in 1890 (Roy, 1890), although for a decade earlier there were studies investigating the change in cerebral blood flow in humans according to different psychological states (Iadecola, 2002). There is considerable evidence that under normal circumstances the brain utilizes glucose as its only source of energy (Jueptner and Weiller, 1995), and as there are only minimal glycogen stores in the brain, a permanent

supply of glucose by the blood is necessary (Clarke, 1994). The evidence is presented that glucose utilization reflects neuronal activity, especially at the synapses (Jueptner and Weiller, 1995), and that regional changes in cerebral blood flow reflect variations in local synaptic activity, as measured using positron emission tomography (PET) (Frackowiak and Friston, 1994; Sokoloff et al., 1977).

PET is a tomographic nuclear imaging procedure using positron emitters, such as positron-labelled water $^{15}\text{H}_2\text{O}$, which is injected intravenously into the patient, in order to detect changes in regional cerebral blood flow (Herscovitch et al., 1983; Raichle et al., 1983).

Functional magnetic resonance imaging (fMRI) also detects the change in cerebral blood flow, but uses the changing ratio of oxyhaemoglobin to deoxyhaemoglobin (Ogawa et al., 1990; Rosen et al., 1998). Oxyhaemoglobin has no magnetic properties, but deoxyhaemoglobin is strongly paramagnetic and can serve as an intrinsic paramagnetic contrast agent (termed the blood oxygenation level dependent (BOLD) contrast), when a strong magnetic field is applied in MRI. As the local cerebral blood flow increases, but without increasing the local oxygen consumption, the venous oxyhaemoglobin concentration will increase and the deoxyhaemoglobin concentration will decrease. As a result there is less paramagnetic influence on the spin of nuclei generated by an externally applied magnetic field, and thus there is less disturbance, and an increase of intensity of the signal (Matthews, 2001).

Voxel Based Morphometry (VBM) was developed as a novel technique for characterising regional cerebral grey and white matter differences in structural magnetic resonance images by the application of methods derived from functional imaging (Wright et al., 1995). It is an automated non-biased whole brain technique which analyses changes in brain structure, involving a voxel-wise comparison of the local concentration of grey matter between two groups of subjects. Specifically in VBM, the structural MR images are spatially normalised to the same stereotactic space, then the grey matter is extracted from the normalised images (segmentation), and then smoothed with an isotropic

Gaussian kernel, in order to make them comparable for specific anatomical differences on a voxel-by voxel basis (Ashburner and Friston, 2000; Mechelli, 2005). VBM has been useful in characterising subtle changes in brain structure in a variety of diseases associated with neurological and psychiatric dysfunction, such as schizophrenia, developmental and congenital disorders, autism, bipolar disorders, temporal lobe epilepsy, supranuclear palsy (Mechelli et al., 2005), cluster headache (May et al., 1999a) and chronic tension type headache (Schmidt-Wilcke et al., 2005).

Statistical parametric mapping refers to the construction and assessment of spatially extended statistical processes used to test hypotheses about functional imaging data, (Friston, 2003) (www.fil.ion.ucl.ac.uk/spm). It is a voxel-based approach, employing classical inference, and was developed to make some comment about regionally specific responses to experimental factors (Friston et al., 1991). The images are pre-processed using realignment, normalisation, and smoothing. The realignment transformation aims to reduce unwanted variance components in the voxel time-series that are induced by movement or shape differences among a series of scans. After realigning the data, a mean image of the series is used to estimate some warping parameters that map it onto a template conforming to a standard anatomical space *e.g.* (Talairach and Tournoux, 1988). The data are then smoothed using a Gaussian smoothing kernel corresponding to the size of the anticipated effect. The spatial scale of haemodynamic responses is, according to high-resolution optical imaging experiments, about 2 to 5mm. Despite the potentially high resolution afforded by fMRI, an equivalent smoothing is suggested for most applications. In the context of inter-subject averaging it is often necessary to smooth more (*e.g.* 8 mm in fMRI) to project the data onto a spatial scale where homologies in functional anatomy are expressed among subjects.

Statistical parametric maps (SPMs) are generated by testing a null hypothesis at each voxel, using a univariate Student's t or F test, and the resulting statistical parameters are assembled into an image which is the SPM. The general linear model is employed to construct a design matrix whereby each voxel is tested for a response Y in terms of a linear combination of explanatory variables X plus a well behaved error term ε :

$$Y = X\beta + \varepsilon \text{ (Friston et al., 1995b).}$$

Variables may be tested with parametric modulation; that is the test is performed on each voxel for the variable as it changes with time, or severity of pain, and this can be done either in a linear fashion (polynomial order = 1), or a nonlinear fashion (polynomial order > 1). Each column of the design matrix corresponds to an effect, also known as a parameter, which may be part of the experiment, or which may be an unwanted effect such as movement of the hand to press the keypad, and will confound the results unless it is accounted for in the design matrix and 'modelled out' of the results of interest. An example is shown in Figure 11.1. The relative contribution of each of these columns is assessed using standard least squares and inferences about these contributions are made using t or F statistics, depending upon whether one is looking at a particular linear combination (*e.g.* a subtraction), or all of them together. When assessing a particular effect, a contrast vector is set up; so in this example the contrast vector [0 1 0 0 0] assesses the second column, which corresponds to headache as parametrically assessed with the intensity of the pain.

The significance of each contrast is assessed with a statistic that has Student's t distribution under the null hypothesis. For each contrast or difference in parameter estimates, a SPM $\{t\}$ statistic is generated for each voxel in the brain. This is transformed into a SPM $\{Z\}$. Statistical inferences are then made about local excursions of the SPM $\{Z\}$, using the Gaussian field theory (Worsley et al., 1992). The resulting P values and the SPM $\{Z\}$ scores are the endpoint of the analysis.

2.3 Functional Imaging in Primary Headache Syndromes

2.3.1 Migraine

Migraine with aura

Migraine aura is the complex of reversible neurological symptoms that occur just before or at the onset of the headache. Aura usually involves visual, sensory or speech

symptoms, and develops gradually over 5-20 minutes and lasts less than 60 minutes (Headache Classification Committee of The International Headache Society, 2004). Cortical spreading depression of Leao (Leao, 1944) has been suggested to underlie migraine visual aura, based on the slow spread of clinical and electrophysiological events in animal experiments (Lauritzen, 1987; Mraovitch et al., 1992). The advent of functional imaging has allowed the testing of this hypothesis in humans.

Using intra-arterial $^{133}\text{Xenon}$ blood flow studies, Olesen and colleagues (Friberg et al., 1994; Olesen, 1991; Olesen et al., 1981) showed a focal reduction of regional cerebral blood flow (rCBF) during aura- like symptoms, usually in the posterior parts of one hemisphere. These changes were produced by carotid angiography, but similar changes have been seen in spontaneous attacks with single photon emission computer tomography (SPECT) (Lauritzen, 1994) and perfusion-weighted magnetic resonance imaging (Cutrer et al., 1998). Areas of hypoperfusion in the frontal cortex have also been observed, both with and without simultaneous reductions in posterior parietal and occipital blood flow (Friberg et al., 1987; Lauritzen et al., 1983). However symptomatic patients with no disturbance in rCBF have been observed in some series (Lauritzen et al., 1983).

A recent study using high-field functional MRI during visual aura in three subjects demonstrated BOLD signal changes which were time-locked to precept/onset of the aura, and which progressed slowly over the occipital cortex in line with the retinotopy of the visual percept of the aura (Hadjikhani et al., 2001). A recent PET study has demonstrated activation in the primary visual area of the occipital cortex in migraine aura which was reproducibly triggered by nitroglycerin (Afridi et al., 2005a).

Hemiplegic Migraine

A case of sporadic hemiplegic migraine showed SPECT evidence of increased cerebral blood flow in the contralateral hemisphere, consistent with hyperperfusion (Barbour et al., 2001). Hyperperfusion has also been demonstrated in a patient with familial hemiplegic migraine (FHM), using multimodal MRI including diffusion-weighted (DWI) and perfusion-weighted (PWI) imaging, and FADS (factor analysis of dynamic studies)

(Lindahl et al., 2002). A PET investigation in a patient with FHM revealed glucose-hypometabolism in the fronto-basal cortex, caudate nucleus and thalamus on the side contralateral to the hemiplegia (Gutschalk et al., 2002). However, MRI including PWI and DWI were normal in the same patient.

Migraine without aura

In 1994, Woods and colleagues published the first report of PET measurements in a patient from the start of a spontaneous migraine attack of unilateral headache without aura but with visual blurring, whilst lying in the PET scanner for another purpose (Woods et al., 1994). There was bilateral reduction in rCBF in the visual association cortex, and this decrease spread contiguously across the cortical surface at a relatively constant rate, sparing the cerebellum, basal ganglia and thalamus. Most of the changes were relatively short-lasting, with substantial recovery by the time of the next scan (12-15 minutes). These findings are in contrast with SPECT studies (Lauritzen and Olesen, 1984; Olesen, 1991; Olesen et al., 1982) in which no changes in rCBF in migraine attacks without aura were demonstrated. However given the difficulties of reporting the visual changes in a PET scanner environment, it is not clear whether or not the subject experienced true aura.

Migraine without aura and CBF

In contrast to migraine with aura, blood flow is usually normal and symmetrical both ictally and interictally in migraine without aura (Olesen et al., 1990; Olesen et al., 1982). However a SPECT study by Friberg *et al* demonstrated abnormal interhemispherical asymmetries in rCBF interictally in almost 50% of patients (Friberg et al., 1994a). The authors concluded that, at least interictally, a cerebrovascular dysregulation existed. This has been corroborated by other groups (Mirza et al., 1998). In a study combining rCBF and blood flow velocity in the middle cerebral arteries using transcranial Doppler sonography, it was found that middle cerebral artery (MCA) velocity on the headache side was significantly lower than that on the non-headache side, returning to normal values after treatment with sumatriptan (Friberg et al., 1991). It was concluded at the time that the headache phase was associated with a dilation of the MCA on the headache side which was reversed by the vasoconstrictor action of the 5HT_{1B/1D} agonist sumatriptan.

However, as the cerebral blood flow was unaffected, no evidence for an important vascular role was established (Goadsby, 2001b). Consistent with the lack of a correlation are transcranial Doppler findings that the vasoconstrictor effect of sumatriptan is not temporally related to headache relief (Limmroth et al., 1996). Moreover it has been recently shown that sildenafil can induce migraine via a cGMP-dependent mechanism, without initial dilation of the MCA (Kruuse et al., 2003); thus refuting the theory that migraine is primarily a vascular headache.

Migraine and PET

Animal studies indicating that dysfunction in brainstem nuclei involved in sensory modulation, including antinociception and craniovascular control, may account for the pathophysiology of migraine (Goadsby et al., 1991; Lance et al., 1983). It has been postulated that the brainstem plays a central role in the pathogenesis of migraine (Goadsby et al., 1991; Welch et al., 2001).

Weiller et al (Weiller et al., 1995) studied patients with migraine without aura using PET, and found significantly higher rCBF values during an attack compared to the headache-free state in brainstem structures over several planes. These structures were towards the midline but contralateral to the headache side, and have since been refined in their localisation to the dorsal pons (Bahra et al., 2001). It has been speculated that the contralateral changes may represent rostral, rather than caudal, control systems (Goadsby and Fields, 1998). There was also activation in the antero-caudal cingulate cortex and in visual and auditory association cortices; these activations were abolished with abortion of the attack by subcutaneous sumatriptan, but the activation in the medial brainstem persisted (Weiller et al., 1995). It can therefore be deduced that the observed activation in the brainstem was unlikely to be just the result to pain perception or increased activity of the endogenous anti-nociceptive systems (May, 2003), and that the brainstem may indeed be the ‘generator’ of the attacks.

A PET scan in a patient with both migraine and CH during a migraine attack, while he was in an active cluster period, showed brainstem activation in the dorsal rostral pons

(Bahra et al., 2001), and dorsal rostral pontine activation at virtually the same locus has been demonstrated in a PET study in chronic migraine (Matharu et al., 2004a). This was reinforced in a group of patients with episodic migraine where activation of the dorsolateral pons on the left side was noticed during acute migraine, and associated deactivation of the contralateral pons (Afridi et al., 2005b), as well as the 'pain matrix' such as the anterior cingulate, prefrontal cortex, and insula, which were consistent with areas seen during studies involving acute pain, and the thalamus contralateral to the side of pain, which is consistent with known anatomy (Bingel et al., 2003). Furthermore, a PET study in spontaneous migraine showed activation in the ipsilateral cingulate cortex, bilateral insulae, cerebellum, brainstem (including midline and contralateral midbrain, and dorsal midline pons), and also in the ipsilateral hypothalamus when comparing the attack to the painfree state; and after pain relief with subcutaneous sumatriptan, the hypothalamic, brainstem and ipsilateral cerebellar activations persisted (Denuelle et al., 2004), thus strengthening the evidence that these structures are involved in the migraine attack and are not just activated in response to pain.

Experimental evidence has emerged that supports a role for the brainstem in the pathogenesis of migraine. The brainstem, specifically the periaqueductal grey matter (PAG), is involved in the inhibition of trigeminovascular specific nociception traffic. Stimulation of the ventrolateral PAG produces inhibition of nociceptive signals (Knight and Goadsby, 2001), while blockade of P/Q type voltage gated calcium channels (Ophoff et al., 1996), known to be involved in familial hemiplegic migraine, is pronociceptive (Knight et al., 2002). The L- and T-type calcium channel blocker flunarizine has been reported as beneficial in migraine without aura (Ciancarelli et al., 2004) and hemiplegic migraine (Silver and Andermann, 1993; Tobita et al., 1987) and the L-type calcium channel antagonist verapamil had a good effect in hemiplegic migraine (Yu and Horowitz, 2003).

Further evidence for the importance of the brainstem in the initiation of migraine is provided by the presence in the brainstem of binding sites for specific anti-migraine compounds such as dihydroergotamine (Goadsby and Gundlach, 1991) and zolmitriptan

(Goadsby and Knight, 1997). There is clinical evidence from a report of non-migraine patients who developed migraine-like episodes after stereotactic intervention to the PAG which responded to 5HT_{1B/1D} agonists (Raskin et al., 1987; Veloso et al., 1998). A multiple sclerosis plaque in the PAG (Haas et al., 1993), a midbrain arteriovenous malformation (Goadsby, 2002a) and a brainstem cavernoma (Afridi and Goadsby, 2003) have been reported to produce migraine-like headaches.

Migraine and MRI

Cao et al (Cao et al., 2002) used functional MRI-BOLD in a series of patients with visually-triggered migraine, and showed increased signal in the red nucleus and substantia nigra before occipital cortex signal elevation or the onset of visually triggered symptoms in 75% of the patients. Having previously documented bilateral activation of these areas in spontaneous migraine with aura (Welch et al., 1998), they concluded that these brainstem structures are part of a neuronal network in the brainstem which initiates the migraine attack. Studies using high-resolution MRI to measure iron homeostasis in the PAG found that it was selectively, progressively and persistently impaired in patients with episodic migraine and chronic migraine, thus emphasising the role of the PAG as a possible generator of migraine attacks, potentially by dysfunctional control of the trigeminovascular nociceptive system (Kruit et al., 2002; Welch et al., 2001)

2.3.2 Cluster Headache

The stereotypical attacks of unilateral pain with associated cranial autonomic symptoms, lasting 15-180 minutes (Headache Classification Committee of The International Headache Society, 2004) should make CH relatively easy to identify, but many go undiagnosed and suboptimally treated (Bahra and Goadsby, 2004). One reason for this is that until recently, there has been little known of the pathophysiology of these headaches. Given the strong circadian rhythmicity of the headache attacks (Russell, 1981), and the often seasonal variation of the bouts of episodic CH (Kudrow, 1987), it has been suggested that a central neuronal origin such as the hypothalamus may be the generator of the headaches (Cohen and Kaube, 2005; Goadsby, 2002b).

Cerebral Blood Flow Imaging and Cluster Headaches

Various studies have been performed including SPECT and ^{133}Xe inhalation (Krabbe et al., 1984; Nelson et al., 1980; Norris et al., 1976), and have shown heterogeneous results, with reports of high, or low, or no change, in cortical blood flow. Methodological differences probably account for these conflicting results. A single photon emission tomography (SPET) study (Di Piero et al., 1997) showed altered responses in rCBF in CH sufferers, which may reflect a marker of the biological modification of the pain system. These occurred even out of the cluster headache bout, and therefore were proposed to indicate the involvement of central tonic pain mechanisms in the pathogenesis of CH.

PET studies and CH

In a small study, Hsieh et al. (Hsieh et al., 1996a) reported activation in the non-dominant anterior cingulate cortex (ACC) in nitroglycerin-induced CH attacks; as would be expected, since in most human PET studies of pain, activation of this region is observed, perhaps as a part of the affective response (Derbyshire et al., 1997). In a larger series there was activation ascribable to the acute CH induced by nitroglycerin in the ipsilateral posterior hypothalamic grey matter, when compared to the headache-free state (May et al., 1998a). This highly significant activation was not seen in cluster headache patients out of the bout when compared to patients experiencing an acute attack (May et al., 2000). Moreover, there was no change in the brainstem, midbrain or pons, as has been reported for migraine. In one patient with both CH and migraine, whose attack was captured by PET, the phenotype of the attack (migraine without aura) matched the functional activation result (pontine change) without any hypothalamic activation (Bahra et al., 2001). This makes the point that although migraine and CH may share a common pain pathway, the trigeminovascular innervation, their underlying pathogeneses are probably significantly different, as indicated by their different clinical phenotypes and responses to preventive medications (Goadsby, 1997b; Lance and Goadsby, 2005).

Furthermore no hypothalamic activation was seen in experimental pain induced by capsaicin injection into the forehead (May et al., 1998b), which would activate first division (ophthalmic) afferents that are the trigeminal division predominantly responsible for pain activation in cluster headache. This plus the strong circadian and seasonal rhythmicity, implies that the hypothalamus is the primary generator of the cluster headache attacks, rather than simply representing a response to pain in the first trigeminal division.

A PET study showed posterior hypothalamic activation during a spontaneous CH attack in a patient who had undergone stereotactic deep brain hypothalamic stimulation, after the stimulator was switched off (Sprenger et al., 2004). The beneficial effect of hypothalamic stimulation in intractable CH has strengthened the clinical role of the hypothalamus in these syndromes (Franzini et al., 2003; Leone et al., 2004a; Schoenen et al., 2005).

Morphometric Studies

A fundamental tenet of primary headache syndromes is the view that they are due to abnormal brain function with normal brain structure. Voxel-based morphometry (VBM) is an automated non-biased whole brain technique which analyses changes in brain structure (Ashburner and Friston, 2000). Used to study the structure of brains in patients with cluster headaches, a significant structural difference in grey matter corresponding to an increase in volume in the ipsilateral posterior hypothalamic grey was noted, when compared to healthy volunteers (May et al., 1999a). This provides further co-localisation of morphometric and functional changes to the hypothalamus which has been previously considered on clinical and neuroendocrine grounds to be specific to cluster headache. A decrease in grey matter was found in patients with chronic tension type headache in the dorsal rostral and ventral pons, the anterior and posterior cingulate cortices, the anterior and posterior insulae, the posterior temporal lobe, the orbitofrontal cortex and parahippocampus and the cerebellum (Schmidt-Wilcke et al., 2005). It is interesting to note that there have been no such changes observed in the same study in patients with

medication overuse and a history of migraine. In a separate study using VBM in migraine, no changes in the structure of the brain were noted (Matharu et al., 2003b).

2.3.3 Other Trigeminal Autonomic Cephalgias

The involvement of trigeminal pathways in PH and SUNCT, and particularly the episodic nature, unilaterality and autonomic features in SUNCT similar to those in CH, have led to investigations into elucidating a common neural pathogenesis for the TACs, likely the hypothalamus.

A study involving transcranial Doppler ultrasonography demonstrated an interhemispheric asymmetry in blood flow velocity in the middle cerebral artery, with vasodilation coinciding with attack onset (Poughias and Aasly, 1995). However SPECT analysis demonstrated normal tracer uptake and symmetrical hemispheric perfusion. It was thought that the brevity of the attacks in SUNCT probably did not allow rCBF differences to be established. In contrast, using fMRI in 6 consecutive spontaneous pain attacks in a patient with SUNCT, activation was seen in the ipsilateral inferior posterior hypothalamic grey when compared to the resting state (May et al., 1999b). The BOLD contrast signal closely tracked the patient's reported pain which came in attacks every 2-3 minutes. The activation in the hypothalamus was seen solely in the pain states as was activation bilaterally in the thalamus and insulae. These results further suggest that trigeminal activation can be associated with cranial autonomic activation as a clinical characteristic of primary headaches (Goadsby, 2001b). Bilateral hypothalamic activation has been detected on fMRI in SUNCT (Sprenger et al., 2005), and the hypothalamus has also been reported in a TAC not otherwise specified, but likely to be longer-lasting attacks of SUNCT (Sprenger et al., 2004b). This has proven to be of clinical use, as deep brain hypothalamic stimulation has relieved a case of drug-resistant SUNCT (Leone et al., 2005).

As the hypothalamic activation was in the same area as was demonstrated to be active in cluster headache patients, this may suggest a common pathophysiological substrate between these two syndromes.

A PET study in PH reported activity in the contralateral posterior hypothalamus and the ventral midbrain, extending over the red nucleus and substantia nigra, in association with the headache attacks (Matharu et al., 2006b). There was also persistent activation of the pain neuromatrix such as cingulate cortices, insulae, primary and secondary somatosensory cortices, frontal cortices including the premotor and supplementary motor area temporal cortices, basal ganglia and the cerebellum, during the acute PH attacks and the interictal pain-free state when off indomethacin, which were deactivated by the administration of indomethacin.

2.3.4 Hemicrania Continua

Hemicrania continua, which is neither migraine nor currently classified as a TAC, shares symptoms of both. HC is a strictly unilateral, continuous headache of moderate intensity, with superimposed exacerbations of severe intensity that may be accompanied by trigeminal autonomic features and migrainous symptoms. A complete response to indomethacin is a prerequisite for diagnosis by the revised IHS classification criteria (Headache Classification Committee of The International Headache Society, 2004). A recent PET study in HC demonstrated activation of the contralateral posterior hypothalamus, which correlates with hypothalamic activation in CH and the TACs, and also in the dorsal rostral pons, ventrolateral midbrain (extending over the red nucleus and substantia nigra) and pontomedullary junction (Matharu et al., 2004c). The ipsilateral dorsal pontine locus correlates with those previously found to be active in migraine (Bahra et al., 2001; Matharu et al., 2004a). Therefore it can be deduced from clinical and imaging evidence that HC may represent an overlapping of these two syndromes, or even a distinct syndrome with phenotypic overlay reflected in the areas of brain activation. Its absolute response to indomethacin, a similarity shared with PH, may in part be due to the

activation of the ventral midbrain, red nucleus and substantia nigra, which is active in the painful phases in both conditions and inactive after treatment with indomethacin.

2.4 Brainstem activation

Brainstem activation in functional imaging studies of head pain, hitherto, seemed specific for migraine, given that it had not been observed in acute CH (May et al., 1998a), SUNCT syndrome (May et al., 1999b), atypical facial pain (Derbyshire et al., 1994) and experimentally-induced facial pain (May et al., 1998b). However brainstem activation has been recently reported in cluster headache (Sprenger et al., 2004a), although a significance analysis was not performed on this region.

In terms of non-headache pain, evidence from both human and animal studies has demonstrated a key role for brainstem centres in the control of ascending nociceptive input (Brooks and Tracey, 2005). The PAG is also known to have an inhibitory effect on the nociceptive response to trigeminovascular activation (Knight et al., 2005). The PAG and the rostral ventromedial medulla have been shown to be active during somatic and visceral pain, with the PAG activity correlating with the subjects' anxiety (Dunckley et al., 2005b). Activity in the mesencephalic reticular formation in the region of the nucleus cuneiformis and PAG was demonstrated in allodynia (Petrovic et al., 1999) and a paradigm of somatic secondary hyperalgesia (Zambreanu et al., 2005).

Further studies will help to elucidate whether this region is indeed specific for migraine, or whether it has a more general role in the modulation of nociceptive traffic. Given the primary inhibitory role of the PAG in modulating trigeminovascular nociception (Knight et al., 2002; Knight and Goadsby, 2001), it may be that a dysfunction within the PAG, such as the P/Q-type calcium channels that are dysfunctional in familial hemiplegic migraineurs (FHM) (Ophoff et al., 1996), may cause a reduction in the PAG-mediated antinociceptive effect and a heightened pain state as seen in migraine. This would correlate with the finding of pontine activation with deactivation in the contralateral pons during migraine (Afridi et al., 2005b); it may be that the nociceptive inhibitor is

hypofunctioning on one side. Other areas of the brainstem suggested to be involved in migraine, namely the locus ceruleus and dorsal raphe, form part of the antinociceptive network and are involved in cerebrovascular control (Lance et al., 1983). The serotonergic and noradrenergic systems are also involved in the modulation of cortical activity and attentiveness to environmental stimuli (Parvizi and Damasio, 2003). This may help to explain the so-called associated symptoms of migraine, such as photophobia and phonophobia (Afridi et al., 2005b).

2.5 The Hypothalamus, CH and TACs

The striking circadian and circannual periodicity in CH implicates a role for the suprachiasmatic nucleus of the hypothalamic grey matter, which is the area involved in the human biological clock system (Albers et al., 1984; Moore-Ede, 1983). The hypothalamus is known to regulate circadian (and seasonal) rhythms, through the suprachiasmatic nucleus (SCN) (Ralph et al., 1990), with information about the level of ambient light through the retino-hypothalamic tract (Reppert and Weaver, 2002). Photoc information relayed from the SCN to the pineal gland is closely reflected there in the secretion of melatonin, which is low during the day and increases during the hours of darkness (Brzezinski, 1997; Utiger, 1992).

Neuroendocrine studies provided the first evidence of deranged hypothalamic function in CH. It was initially demonstrated that plasma testosterone concentrations were altered during the CH period in men (Kudrow, 1976). Subsequently, it has been observed that there are abnormalities in the secretion of melatonin and cortisol, alterations in the secretion of luteinising hormone and prolactin, and altered responses of luteinising hormone, follicle stimulating hormone, prolactin, growth hormone, and thyroid stimulating hormone to challenge tests in patients with CH (Leone and Bussone, 1993). Treatment with melatonin reduced headache frequency in episodic (Leone et al., 1996), and chronic CH sufferers (Peres and Rozen, 2001), and high-dose steroids can have a beneficial effect in CH (Antonaci et al., 2005; Couch and Ziegler, 1978). These treatments may be addressing the imbalance in melatonin and cortisol secretion,

respectively. A male patient with SUNCT with low serum testosterone had beneficial effects on treatment with clomiphene, which raised his testosterone levels (Rozen et al., 2005). It was postulated by the authors that the clomiphene acted directly on hypothalamic oestrogen receptors to modulate hypothalamic activity and thus suppress SUNCT attacks.

Deep brain electrical stimulation of the posterior hypothalamus has had beneficial effects in both intractable CH (Leone et al., 2004a) and SUNCT (Leone et al., 2005). Moreover, observations from psycho-surgery suggest that stimulation of the posterior hypothalamic region initially produces agitation and restlessness, and necessitates a general anaesthesia (Bejjani et al., 2002; Sano et al., 1970). This is a remarkable observation given that such behaviour is typical in up to 93% of patients' acute cluster headache attacks (Bahra et al., 2002). Taken together, the clinical observations, neuroendocrine studies, functional and structural imaging data, and the neuromodulation studies strongly suggest a pivotal role for the hypothalamus in CH.

However, in functional imaging studies and deep brain stimulation, the area activated and stimulated is the posterior hypothalamus, which is anatomically distinct from the suprachiasmatic nucleus. This, together with the mechanism by which the hypothalamic activation may induce pain, gives rise to the question that hypothalamic activation may not be the direct perpetrator of the painful attacks. The issue then remains: functional imaging demonstrates hypothalamic activation during attacks of these headaches, but this may be an association rather than a direct causation, and the hypothalamic link between the attacks and sleep may not be as direct as previously thought.

The hypothalamus may play a role in other headache syndromes such as migraine. It has been noticed that 55-63% of migraine sufferers can be woken at night or in the morning with headache (Galego et al., 2002), and migraine patients prior to an attack may show sleep disturbances (Goder et al., 2001), changes of wakefulness and alertness (Dalkvist et al., 1984), as well as changes of appetite (Blau, 1980), which would all implicate hypothalamic involvement. Furthermore there is biochemical (Peres et al., 2001) and

functional imaging (Denuelle et al., 2004) evidence for hypothalamic involvement in migraine. Thus the delineation between migraine and TACs in terms of brainstem or hypothalamic function, and also the role of the hypothalamus in different headache syndromes with varying degrees of circadian rhythm, needs to be elucidated.

Activation in the region of the hypothalamus has been reported in other pain studies (Ingvar, 1999; Jones et al., 2003; Kupers et al., 2000; Sanchez del Rio and Alvarez Linera, 2004), not specifically head pain. Significant hypothalamic activation has been reported in experimental arm pain (Hsieh et al., 1996a) and anginal pain (Rosen et al., 1994), although there was no significant difference between painful and painless myocardial ischaemia (Rosen et al., 1996). A single case report PET study on a patient with neuropathic facial pain treated with thalamic stimulation for pain control showed hypothalamic activation when scans of the painful state were contrasted with the pain-free state immediately after stimulation; post-stimulation analgesia has been attributed to activation of central structures beyond the stimulation period (Linderoth, 2002; Roberts and Rees, 1986), making the significance of the hypothalamic activation hard to interpret. Several studies of acupuncture stimulation at analgesic points in pain-free volunteers have reported hypothalamic activation (Hui et al., 2000; Wu et al., 1999; Wu et al., 2002). It is noted that the hypothalamic area activated in all these studies is a different area than that reported in CH (May et al., 1998a).

It is interesting to observe that the clinical feature that is common to the four primary headache syndromes in which posterior hypothalamus activation has been reported (i.e. PH, CH, SUNCT and HC) is prominent cranial autonomic features in association with the headache. It has been suggested that the pathophysiology of these syndromes revolves around the trigeminal-autonomic reflex (Goadsby and Lipton, 1997). There is considerable experimental animal literature to document that stimulation of trigeminal efferents can result in cranial autonomic outflow, the trigeminal-autonomic reflex (May and Goadsby, 1999). In fact, some degree of cranial autonomic symptomatology is a normal physiologic response to cranial nociceptive input (Frese et al., 2003; May et al., 2001) and patients with other headache syndromes, such as migraine, may report these

symptoms (Barbanti et al., 2002; Benoliel and Sharav, 1998). The distinction between these and other headache syndromes is the degree of cranial autonomic activation. It has been suggested that the cranial autonomic symptoms may be prominent in these syndromes due to a central disinhibition of the trigeminal-autonomic reflex by the hypothalamus (Benjamin et al., 2004). Indeed there are direct hypothalamic-trigeminal connections (Malick and Burstein, 1998), and the hypothalamus is known to have a modulatory role on the nociceptive and autonomic pathways, specifically trigeminovascular nociceptive pathways (Bartsch et al., 2004). Hence, the posterior hypothalamic activation observed in this study provides further support for the notion that this structure may have a crucial role in the pathophysiology of TACs and HC (May and Goadsby, 1999).

How do these data inform the role played by posterior hypothalamic activation observed in TACs and HC? The weakness of functional imaging techniques is that they provide regions of significant change on brain volumes without directional information about the ascending or descending nociceptive inputs from which these changes result (Jones et al., 2003). They can, therefore, only be interpreted with reference to clinical, anatomical, biochemical, electrophysiological and pharmacological studies derived from animal and human studies. With the currently available data on these syndromes, it remains inconclusive whether the posterior hypothalamic activation is central or epiphenomenal to the pathophysiology of the TACs.

2.6 Experimental Head Pain

The PET study by May *et al* in nitroglycerin-induced CH attacks (May et al., 1998a) reported activation in areas which fell into three categories: the hypothalamus which is specific to CH attacks, areas generally associated with pain, and vascular structures. The areas associated with pain were the non-dominant ACC, the frontal cortex and insulae, and the ventroposterior thalamus contralateral to the side of the pain.

The same group investigated healthy males with no history of headache, during an experimental pain state by injecting capsaicin subcutaneously in the forehead to evoke a

painful sensation in the first division of the trigeminal nerve (May et al., 1998b). During the acute pain state compared to the resting state, increases in rCBF were found bilaterally in the anterior insula, the contralateral thalamus, the ipsilateral anterior cingulate cortex and bilaterally in the cerebellum. Activation of the ACC has been repeatedly reported in PET studies on the sensation of somatic or visceral pain and attributed to the emotional response to pain (Casey et al., 1994; Hsieh et al., 1996a; Jones et al., 1992). Activations in the insula have been demonstrated in previous studies following application of heat (Casey et al., 1994; Coghill et al., 1994), subcutaneous injection of ethanol (Hsieh et al., 1996b), somatosensory stimulation (Burton et al., 1993), and during cluster headache (Hsieh et al., 1996a) and atypical facial pain (Derbyshire et al., 1994). The insula is known to be involved in the regulation of autonomic responses, and has been suggested to relay information to the limbic system (Mesulam, 1985). Activation of the contralateral thalamus due to pain is known from experimental animals (Goadsby, 1997a) and functional imaging studies in humans (Casey et al., 1994; Davis, 2000; Derbyshire et al., 1994). However there was no activation reported in the capsaicin-induced pain in the brainstem, as compared to spontaneous migraine (Weiller et al., 1995), or in hypothalamus as in nitroglycerin-induced CH attack (May et al., 1998a). This confirms that the activations seen in these primary headache syndromes are specific to these syndromes and not purely as a result of first division trigeminal pain.

A functional MRI study to compare facial pain representation for different divisions of the trigeminal nerve showed activation in contralateral somatosensory cortices, with bilateral activation for V₁ (ophthalmic) division pain, but there was no mention of change in brainstem or hypothalamic activity (Iannetti et al., 2003).

2.7 Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopic (MRS) studies have arisen in migraine on the basis of evidence of abnormal cortical information processing in electrophysiological studies (Afra et al., 1998; Wang et al., 1996), and decreased mitochondrial energy reserve from

MRS studies in migraine with (Barbiroli et al., 1992; Welch et al., 1989) and without aura (Montagna et al., 1994). ³¹Phosphorus MRS can ascertain abnormalities in energy metabolism as reduced levels of phosphocreatine, reduced cellular-free energy and increased rate of adenosine triphosphate (ATP) biosynthesis. Abnormalities in energy metabolism were found interictally, and not necessarily selective to brain but also in extraneural tissues such as muscle (Montagna, 1995; Montagna et al., 1994). The authors concluded that these abnormalities in energy metabolism, particularly a generalised disorder of mitochondrial oxidative phosphorylation, predisposed migraineurs to develop an attack triggered by conditions of increased brain energy demand.

Proton MRS has also shown metabolic abnormalities in migraineurs, with high lactate levels in the interictal period (Watanabe et al., 1996), thus suggesting that anaerobic glycolysis occurs in the brains of patients with migraine during the interictal period, although a long attack-free period could normalise the subclinical disturbance. It has been suggested (Schoenen, 1994; Schoenen, 1998) that as well as reduction in mitochondrial energy reserve, a reduced habituation of information processing may cause excessive cortical activation. These two mechanisms may induce biochemical shifts, leading possibly via cortical spreading depression (Bolay et al., 2002), to migraine attacks by means of activation of the trigeminovascular system (Moskowitz et al., 1993). Clinically the schema of aura triggering migraine headaches seems unlikely (Goadsby, 2001a).

A recent study using functional magnetic resonance spectroscopic imaging showed high baseline levels of lactate in the occipital region, and an abnormal response to visual stimulus in patients with migraine with visual and motor or sensory aura (Sandor et al., 2005b). This would be compatible with an abnormal metabolic strain during stimulation, possibly due to dishabituation, and a predominant mitochondrial dysfunction in migraine with aura.

Mitochondrial impairment has been shown in proton spectroscopy of skeletal muscle in migraine and cluster headache (Lodi et al., 1997), and in cluster headache brains (Lodi et al., 1997; Montagna et al., 1997). A reduction in free magnesium was found in brains of

migraine and CH patients, with the greatest reduction in keeping with the severity of the clinical state in migraine (Lodi et al., 2001). The authors concluded that this was secondary to the bioenergetics deficit in tissues with mitochondrial dysfunction.

Mitochondrial dysfunction has also been suggested by the response by migraine patients to riboflavin prophylaxis (Schoenen et al., 1994), the nitric-oxide scavenger hydroxycobalamin (van der Kuy et al., 2002), Coenzyme Q (Sandor et al., 2005a), and magnesium (Peikert et al., 1996), although a recent trial showed no statistical difference between riboflavin and magnesium and placebo (Maizels et al., 2004). These all point to the suggestion that abnormalities in energy metabolism predispose migraine and cluster headache sufferers to develop an attack under conditions of increased energy demand, and that treatment with protagonists of the cellular respiratory cycle, such as the aforementioned vitamins, may be effective by reducing the oxidative stress (Montagna, 2002). High-flow oxygen, which is effective in the abortive treatment of CH (Fogan, 1985; Kudrow, 1981), and in hyperbaric pressures in migraine with aura (Wilson et al., 1998), may exert a therapeutic effect reducing oxidative stress and promoting cellular respiration.

2.8 Functional or Metabolic Abnormality?

The presence of mitochondrial abnormalities suggests a hereditary component to migraine. A multinational study of sets of twins indicates a contribution of genes to the liability of migraine (Mulder et al., 2003). Indeed the genetics of migraine, mainly familial hemiplegic migraine, are well documented (De Fusco et al., 2003; Dichgans et al., 2005; Haan et al., 2005; Ophoff et al., 1997; Ophoff et al., 1996; Terwindt et al., 1998). Cluster headache has also been reported with family histories, although to a lesser extent than migraine (Leone et al., 2001; Russell, 2004; Russell et al., 1996; Russell et al., 1995a; Russell et al., 1995b). There have also been reports of family histories in PH (Cohen et al., 2006) and SUNCT (Gantenbein and Goadsby, 2005).

This has to be reconciled with the functional imaging work showing activation of brainstem structures in migraine, and hypothalamus in the TACs. It is possible in migraine that an external trigger may cause an oxidative stress in an already metabolically hypofunctioning brain. The attack itself will be generated or facilitated through the brainstem and dorsal rostral pons, leading to more widespread changes, especially in the occipital region with visual auras, as the attack develops.

Functional imaging shows only an association between the activation in a particular area and the clinical features at that time. In CH, it is possible that the hypothalamic activity seen on functional imaging may not be a direct generator of the CH attacks, and that an abnormality in hypothalamic function facilitates a cascade of metabolic and other biochemical events, including deranged melatonin, cortisol and 5HT metabolism (Cohen and Kaube, 2005), which in turn would trigger an attack in a brain already compromised by abnormal metabolic activity.

Chapter 3

Aims and Objectives

This project is a set of studies to explore aspects of TACs as primary headache syndromes, with an emphasis on SUNCT and SUNA, from a phenotypical, treatment and functional imaging point of view.

3.1 Phenotype of SUNCT and SUNA

The aim of this prospective study is to ascertain and further clarify the clinical and phenotypic characteristics of SUNCT and SUNA, in terms of the International Headache Society Classification of these syndromes (Headache Classification Committee of The International Headache Society, 2004), and to make comments about these syndromes based on a large clinical population of 52 patients with SUNCT and SUNA.

3.2 Treatment of SUNCT and SUNA

The aim of this study was to record and assess the response of a large clinical population of patients with SUNCT and SUNA to medications and treatments. These included:

- 1) abortive attack therapies: inhaled oxygen, intranasal lidocaine and subcutaneous sumatriptan
- 2) short-term preventive therapies:
 - a. intravenous lidocaine and intramuscular indomethacin
 - b. a single-blinded placebo-controlled indomethacin test (the modified *Indotest*) was performed in 14 patients
- 3) preventive therapies:
 - a. double-blind placebo controlled trial of lamotrigine
 - b. double-blind placebo controlled trial of topiramate
 - c. open-label trials of lamotrigine, topiramate, gabapentin, carbamazepine, and others including other neuromodulators, melatonin, verapamil,

corticosteroids, non-steroidal anti-inflammatory drugs, adrenoreceptor blockers, serotonergic agonists and antagonists, tricyclic antidepressants and lithium

- 4) non-pharmacological interventions:
 - a. greater occipital nerve injections
 - b. local nerve blockades
 - c. invasive surgical procedures involving the trigeminal nerve.

3.3 Functional Imaging in SUNCT and SUNA

The aim of this study was to elucidate the involvement of the hypothalamus in SUNCT and SUNA, by means of functional magnetic resonance imaging and voxel-based morphometry.

The hypotheses are:

- 1) there is activation in the region of the posterior or anterior hypothalamus during attacks of SUNCT and SUNA
- 2) this activation increases in correlation with the level of severity of the pain
- 3) there is a structural difference in grey matter in the region of the hypothalamus between SUNCT/SUNA patients and healthy controls, as measured by voxel-based morphometry.

PART II. CLINICAL STUDIES IN SUNCT AND SUNA

Chapter 4

Clinical Studies in SUNCT and SUNA

4.1 Introduction

SUNCT, Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing, is a rare primary headache syndrome first described in 1978 (Sjaastad, 1978). The syndrome has been described more fully over subsequent years (Pareja and Sjaastad, 1997; Sjaastad et al., 1989), although only in small series. It has been suggested that it be grouped together with cluster headache and paroxysmal hemicrania as a Trigeminal Autonomic Cephalgias (TACs) (Goadsby and Lipton, 1997) based on the now classical clinical combination of head pain and activation of cranial autonomic efferents (May and Goadsby, 1999). The syndrome was included in the second edition of the International Headache Classification (Headache Classification Committee of The International Headache Society, 2004), as was a syndrome of SUNA: Short-lasting Unilateral Neuralgiform Headache attacks with cranial Autonomic features. Here the first substantial series of patients with SUNCT or SUNA are described in an attempt to define these conditions better.

4.2 Methods

This study prospectively addresses the clinical characteristics of the syndrome, the management strategies used, including pharmacological manipulations as diagnostic tests, acute abortive therapies, short-term preventive therapies, and outpatient preventive therapies. Most of the preventive medications were given as open-label trials, as patients were generally unwilling to participate in placebo-controlled trials, given the option of

receiving an active drug for their extremely painful conditions which had hitherto been inadequately treated.

Another observation was the time taken from the start of the symptoms to the actual diagnosis of SUNCT and SUNA, the number and types of practitioners whom the patients had seen prior to the final diagnosis, and other diagnoses which had been made, as this would influence the types of treatments which the patients would have received during the course of their illness.

The study group was taken from patients attending the outpatient clinics at the National Hospital for Neurology and Neurosurgery, between 1995 and 2005. Some were seen further when admitted for inpatient investigations. Most patients (49/52) were contacted by telephone after giving their written consent, or gave their consent in the clinic appointment. Of the remaining 3 patients, one contacted the National Hospital by phone directly, and the other two were lost to followup and their medical notes provided the source of information. The study was approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee (ref 03/N107).

4.2.1 Clinical Study of Phenotype of SUNCT and SUNA

In the course of the history taking, for the Phenotype study, each patient was asked the same questions about their SUNCT/SUNA: the side, site and character of their pain; duration, frequency and periodicity of their attacks; triggering and relieving factors; the duration of their symptoms, number and types of practitioners seen prior to diagnosis, personal and family history of headache, and any other medical problems.

The patients' notes were also used for information about previous diagnoses and imaging reports. Where possible relatives, particular partners, were questioned regarding the presence or absence of clinical features during the acute attacks.

4.2.2 Clinical Study of Treatment of SUNCT and SUNA

SUNCT has until recently been considered refractory to treatment. However it has now been shown in open-label trials that neuromodulatory treatments such as lamotrigine (D'Andrea et al., 1999a; D'Andrea et al., 2001; Gutierrez-Garcia, 2002; Leone et al., 2000b; Malik et al., 2002), carbamazepine (Matharu et al., 2003a; Matharu et al., 2004b), topiramate (Kuhn et al., 2005; Matharu et al., 2002; Matharu et al., 2004b; Rossi et al., 2003), and gabapentin (Graff-Radford, 2000; Hunt et al., 2002; Porta-Etessam et al., 2002) have been successful in the preventive treatment of some cases of SUNCT.

For the Treatment study, each patient was asked the same questions about their response to medications and the Modified *Indotest* (100mg intramuscularly with a blinded placebo control); their responses to non-pharmacological treatments; previous medications, current medications, doses, effects and side effects; and also non-pharmacological procedures and alternative therapies. They were asked to categorise the effect of each treatment as one of the following:

- 1) 'none' - no beneficial effect on their symptoms, or making their symptoms worse
- 2) 'mild' – a mild effect on their symptoms but not substantially improved
- 3) 'moderate' - a substantial improvement in their symptoms but the attacks were not entirely suppressed
- 4) 'good' - entire suppression of the attacks

The patients' notes were also used for information about response to medications.

Some patients (10 with SUNCT and 5 with SUNA) were admitted to the National Hospital for Neurology and Neurosurgery for investigation and therapeutic trials of acute abortive and short-term preventive therapies.

Acute abortive therapies:

- 1) Oxygen delivered at high dose and flow (100% at 9-12 litres/min for 15 minutes), through a standard non-rebreathable mask with the air vents taped up to increase

oxygen concentration. One patient also had low flow oxygen (4 litres/ minute) under the care of other doctors, and the response was reported here.

- 2) Intranasal lidocaine 4% delivered to the ipsilateral nostril.
- 3) Sumatriptan 6mg subcutaneously, or 20mg intranasally. Some patients also had oral triptans as abortive therapy as outpatients. These were sumatriptan, rizatriptan and naratriptan, at unknown doses, which were taken previously, and their effects were reported by the patients.

Short-term Preventive Therapies:

- 1) Modified *Indotest* (Matharu et al., 2004b); 100mg indomethacin intramuscularly on one day, with saline placebo injection on another day, in a blinded fashion. The treatments were given in a random order from patient to patient. Each patient kept a diary as to the frequency and severity of the attacks over those days.
- 2) Intravenous lidocaine as a solution in 500ml of 5% dextrose with 2g lidocaine. This was infused at 15-45 ml/hour, which is a rate of 1.5-3.5 mg/kg/hour, starting at the lower infusion rate and increasing on a daily basis, depending on the patient's response in terms of reduction of attacks and side effects. The infusion rate was stopped at whatever dose either reduced the attacks considerably, or until side effects intervened. Each patient was attached to a cardiac monitor for the duration of the infusion in case of cardiac arrhythmia. The patient kept a diary as to the frequency and severity of the attacks during the course of the infusion, and for the duration of the painfree period.

Triggering

Amongst the patients admitted to hospital, 6 SUNCT and 2 SUNA patients received glyceryl trinitrate (GTN) by sublingual spray, on two occasions each, and were observed for the immediate onset of an attack, either of SUNCT/SUNA, or of other headaches in those patients with concomitant migraine.

4.3 Analysis of Results

All results were all collated on a Microsoft Excel® spreadsheet.

Phenotype of SUNCT and SUNA

The following categories were explored:

Epidemiology

- 1) Number of patients with SUNCT and those with SUNA
- 2) Epidemiological factors- age, gender
- 3) Age at onset of the symptoms and duration of symptoms
- 4) Time taken to final diagnosis and previous diagnoses
- 5) Precipitating events in the three weeks prior to their attacks commencing (this differs from the International Headache Society criteria which require the headache to be present at most 7 days after the traumatic event in order to qualify as post-traumatic headache (Headache Classification Committee of The International Headache Society, 2004))
- 6) Personal or family history of migraine

Phenotype

- 7) Laterality and site of the attacks
- 8) Autonomic symptoms and their association with the site of pain
- 9) Type and severity of pain. The patients were asked to rate the severity of their attacks on a verbal rating scale (VRS) of 0 to 10, 0 being no pain at all, and 10 being the most severe pain imaginable, as has been used in migraine studies (de Tommaso et al., 2005; Iversen et al., 1989; Tvedskov et al., 2004)
- 10) Other symptoms, such as agitation, or migrainous symptoms such as worsening by movement, photophobia and phonophobia
- 11) Character of the attacks, length and frequency of the attacks
- 12) Diurnal variation of attacks
- 13) Triggering of attacks and refractory period between attacks
- 14) Periodicity and chronicity of the syndrome

15) Background pain and analgesic overuse in relation to concomitant migraine biology

16) SUNCT and SUNA with abnormal examination and MRI findings- defined as symptomatic SUNCT and SUNA

Treatment of SUNCT and SUNA

For the acute abortive therapies, the primary endpoint for effectiveness was cessation of the attack of SUNCT and SUNA. A moderate effect in that the attack was shortened or the severity was reduced was also considered as 'effective'. Minimal or no effects were considered as 'ineffective'.

For the short-term preventive therapies, the primary endpoint for effectiveness was the suppression of attacks of SUNCT or SUNA for 12-24 hours following the *Indotest*, and for the duration of the lidocaine infusion up to several months afterwards. A moderate effect in that the attacks were reduced in frequency but not totally abolished was also considered as 'effective'. No reduction in the frequency or severity of the attacks was considered as 'ineffective'.

For the long-term preventive therapies, these were all done as outpatients and therefore the diary-keeping was less reliable than those done as inpatients. The primary endpoint for effectiveness was the suppression of attacks of SUNCT or SUNA whilst on a suitable dose of the preventive medication. A moderate effect in that the attacks were mostly suppressed, or that the medication was having a moderate effect at a suboptimal dose which could not be escalated because of side effects, was also considered as 'effective'. Minimal or no effect on the frequency of attacks, or if the attacks were worsened or increased in frequency, was regarded as 'ineffective'.

Triggering

For the GTN triggering, a positive effect was the immediate triggering of an attack of SUNCT or SUNA.

4.4 Double-blind, placebo-controlled crossover trial of topiramate in SUNCT

4.4.1 Introduction

Topiramate is a neuromodulator which is effective in the prevention of migraine as shown in placebo-controlled trials (Brandes et al., 2004; Silberstein et al., 2004) and compared to active treatment (Diener et al., 2004). Its efficacy has been shown in open-label trials in cluster headache (Forderreuther et al., 2002; Lainez et al., 2003; Mathew et al., 2002; Wheeler and Carrazana, 1999), although such a robust response has not been seen in all open-label trials (Leone et al., 2003a). There are isolated case reports of the effectiveness of topiramate in hemicrania continua (Matharu et al., 2006a) and paroxysmal hemicrania (Boes et al., 2003), (Cohen and Goadsby 2006, Paroxysmal hemicrania responding to topiramate; accepted for publication in Journal of Neurology Neurosurgery and Psychiatry, Appendix 2).

Topiramate has been reported to be effective in 6 SUNCT patients at doses up to 300mg daily (Kuhn et al., 2005; Matharu et al., 2002; Matharu et al., 2004b; Rossi et al., 2003), and ineffective in three patients (Black and Dodick, 2002; Koseoglu et al., 2005).

Topiramate is also used in the treatment of other painful conditions, including painful diabetic neuropathy (Pappagallo, 2003; Raskin et al., 2004). It has been reported as useful in intercostal neuralgia (Bajwa et al., 1999), and in a case series of trigeminal neuralgia (Zvartau-Hind et al., 2000), but not in a placebo-controlled study (Gilron et al., 2001).

There have been no double-blind placebo controlled trials of preventives in SUNCT or SUNA, largely because of the rarity of the disease and thus the paucity of patient numbers to enter a research trial. This study aimed to perform a randomised double-blind controlled trial in order to ascertain the effectiveness of topiramate in SUNCT.

4.4.2 Methods

Five male patients (aged 51-72, mean 59.2 years) with SUNCT were recruited from the Outpatient department at the National Hospital for Neurology and Neurosurgery, London. They were diagnosed with SUNCT according to the classification criteria proposed by Goadsby and Lipton (Goadsby and Lipton, 1997), as the study was conducted prior to the International Headache Society classification (Headache Classification Committee of The International Headache Society, 2004). 2 of these had primary chronic SUNCT, 2 had episodic SUNCT, and one had secondary episodic SUNCT. One patient with primary chronic SUNCT had a history of migraine and cluster headache, and has been previously reported as a case report (Empl et al., 2003). The clinical characteristics are given in Table 4.1. They gave their informed consent and were free to withdraw from the study at any time. The study was approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee (reference 00/N072).

Table 4.1
Clinical characteristics of patients in topiramate study

Patient*	Episodic or chronic SUNCT	Other headaches	Mean duration SUNCT attack	Mean number of attacks/day untreated
#47	episodic	nil	120 sec	45
#21	primary chronic	nil	10 sec	>100
#27	secondary chronic	nil	5 sec	85
#34	primary chronic	migraine with aura, cluster headache	1-300sec	>100
#38	episodic	episodic migraine	60 sec	10

* Identification numbers refer to the entire cohort of SUNCT/SUNA patients reported in this series

The design of the study was a randomised, double-blind, placebo-controlled crossover trial. The treatments were identical tablets labelled Treatment 1 and Treatment 2, to be taken in the first and second arm of the study respectively. The order of active treatment and placebo was randomised by the National Hospital's pharmacy, and each participant was assigned a randomisation number. The code was held by the pharmacy until study completion and database locking.

Patients were required to withdraw from preventive medications prior to commencement of the study. After an initial washout drug-free period of 10 days, treatment was started at 12.5mg nightly and increased every 5 days to a maximum of 50mg bd for 10 days, after which the dose was reduced over the next 10 days. A 10 day washout drug-free period followed, after which the patients commenced the second arm of the study in the same paradigm. The patients with episodic SUNCT started the 10 day washout period at the start of their bout.

The patients were instructed to keep a diary for the duration of the study, which documented the date, time, severity and duration of each attack.

4.4.3 Analysis of results

The primary endpoint was the reduction of attack frequency, as measured by the mean daily number of attacks during the 10 days at maximum dose as compared to the 10 drug free days pre-treatment. The results would be analysed on an *n-of-1* basis. Given the large variability in numbers of attacks per day, the change in attack frequency was expressed as a percentage change. A positive result was declared if the attack frequency was reduced by 50% or more. A negative result was declared if the attack frequency was reduced by less than 50%, or indeed if it increased on the treatment as compared to the pre-treatment observation phase.

A secondary endpoint was employed: the 'attack load'; this is the number of minutes of pain per day for each patient. This would take into account the lengthening or shortening of duration of attacks, as these can be variable in SUNCT (see Chapter 5). It would also take into account other types of headache which were experienced during the treatment phases, such as migraine or cluster headache, which are also affected by topiramate (Brandes et al., 2004; Lainez et al., 2003; Silberstein et al., 2004). One patient (#4) had episodic migraine, and one (#8) had migraine and cluster headache as well as SUNCT.

4.5 Double-blind, placebo-controlled trial of lamotrigine in SUNCT/SUNA

4.5.1 Introduction

Lamotrigine is a relatively new anticonvulsant drug effective in partial and generalised tonic clonic seizures. Recently, lamotrigine given in an open-label manner at doses up to 300mg a day has been reported to be highly efficacious in 10 patients with SUNCT (D'Andrea et al., 1999a; D'Andrea et al., 2001; Gutierrez-Garcia, 2002; Leone et al., 2000b; Malik et al., 2002), although it has been reported as ineffective in 4 patients (Black and Dodick, 2002; Matharu et al., 2004b; Sprenger et al., 2005), and ineffective at 400mg a day in a patient with SUNCT related to trigeminal nerve compression (Koseoglu et al., 2005).

4.5.2 Methods

A double-blind, placebo-controlled crossover trial of lamotrigine in SUNCT/SUNA, at doses up to 200mg daily, was started. The trial had been approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee (REC No 02/N132). Patients gave their written consent and were free to withdraw from the trial at any time.

Patients were randomised to receive either lamotrigine or placebo first as Treatment 1. After a 2-week period on no medications, they were to take the medication starting at 25mg daily for 2 weeks, and increasing by 25mg every week to a maximum of 100mg twice a day for two weeks, and then reduce to zero over a period of 3 weeks. After a 2-week washout period, a crossover protocol was performed and the same regime was undertaken as Treatment 2 with either placebo or lamotrigine. Patients were asked to keep a diary from the beginning of the pre-treatment phase to the end of the second treatment, detailing the frequency, severity, duration of attacks, and attack load on a daily basis.

4.5.3 Analysis of Results

The primary endpoint was the reduction of attack frequency, as measured by the mean daily number of attacks during the 10 days at maximum dose as compared to the 10 drug free days pre-treatment. The results would be analysed on an *n-of-1* basis. Given the large variability in numbers of attacks per day, the change in attack frequency was expressed as a percentage change. A positive result was declared if the attack frequency or load was reduced by 50% or more. A negative result was declared if the attack frequency or load was reduced by less than 50%, or indeed if it increased on the treatment as compared to the pre-treatment observation phase.

Chapter 5

Results: Clinical Study of Phenotype of SUNCT and SUNA

5.1 Epidemiology

Of the 52 patients, 31 were male and 21 were female (male:female ratio of 1.5:1). Forty-three of these patients had SUNCT as defined by the International Headache Society (Headache Classification Committee of The International Headache Society, 2004), and nine had syndromes whose cranial autonomic symptoms did not include both conjunctival injection and lacrimation, and whose syndromes were better described as SUNA (Headache Classification Committee of The International Headache Society, 2004). It is not clear whether SUNCT is a sub-group of all SUNA, as suggested by the Classification Committee, or the two are separate. Here they are described separately to act as a basis for further research. Therefore SUNCT patients make up an 83 % subset of all SUNCT and SUNA. There were 28 male and 15 female SUNCT patients (male:female ratio 2:1), and three male and six female SUNA patients (male:female ratio 0.5:1).

5.2 Age of patients and duration of symptoms

At the time of interview, the mean age of patients was 57 years (range 32-87, median 58 years). The mean age at onset of symptoms was 48 for SUNCT (range 19-75, median 48 years). The mean age at onset of symptoms for SUNA was 44 (range 15-57, median 50). The mean duration of symptoms for SUNCT was 10 years (range 2-28 years, median 8 years). The mean duration of symptoms for SUNA was 8 years (range 1-46 years, median 3 years; Table 5.1). It took a mean 6.7 years (range 0.25-24) for SUNCT and mean 7.1 years (range 1-46) for SUNA to be diagnosed. Previous diagnoses included trigeminal neuralgia, cluster headache, paroxysmal hemicrania, TAC otherwise unclassified, hemicrania continua, migraine, and others including stress, psychiatric conditions, shingles, seizures and Bell's palsy. Three SUNA patients had original diagnoses of SUNCT before they were recognized as SUNA (Table 5.2).

Table 5.1

Duration of symptoms and previous diagnoses

	SUNCT	SUNA	SUNCT and SUNA
median age at onset (range)	48 (19-75)	50 (15-57)	48.5 (15-75)
mean duration of symptoms	10	8	9
median duration (range)	8 (2-28)	3 (1-46)	6 (1-46)

Table 5.2

Diagnoses made prior to SUNCT/SUNA, and years to diagnosis

	SUNCT n (%)	SUNA n (%)
TN	18 (42)	1 (11)
CH	11 (26)	1 (11)
PH	4 (9)	4 (44)
TAC	6 (14)	1 (11)
HC	1 (2)	1 (11)
migraine	5 (12)	2 (22)
other	13 (30)	1 (11)
SUNCT	n/a	3 (33)
years to diagnosis	6.7	7.1
median	5	2
range of years to diagnosis	0.25-24	1-46

Some patients went into remission, especially those who had SUNCT or SUNA secondary to a precipitating cause which was treated. One patient (#37) had SUNCT secondary to a prolactinoma (Matharu et al., 2003c). His symptoms started 13 years previously and resolved on cabergoline therapy, so he had been pain free for the last 8 years whilst on treatment and had not tried to stop the cabergoline to see if the attacks recurred. One patient with SUNA (#24) had 14 months of symptoms which then went into spontaneous remission, and she had remained pain free for 3.5 years at the time of interview.

5.3 Precipitating events

Seven patients with SUNCT and two with SUNA had precipitating events in the three weeks prior to their attacks commencing. These involved head or facial trauma in four cases, back trauma in one case, and viral infection, episode of extreme stress, analgesic withdrawal, and cabin pressure changes on an airline flight in each of the others (Table 5.3). One patient (#2) had an episode of severe dizziness, ataxia and headache of sudden onset, which preceded his SUNCT attacks by a few weeks.

5.4 Laterality of attacks

Taking SUNCT and SUNA patients together, 20 (38 %) patients had attacks which were exclusively left-sided, and 22 (42 %) had exclusively right-sided attacks. Five had unilateral, side-variable attacks that affected the left more often than the right side, and three had unilateral, side-variable attacks that affected the right more often than the left. One SUNCT patient had unilateral attacks which could affect the left or right side in equal proportions, and one SUNCT patient had bilateral attacks. In SUNCT there were slightly more right than left sided attacks (47 % versus 33 %, respectively), whereas in SUNA there were more left than right sided attacks (67 % right, 22 % left; Table 5.4).

Table 5.3
Precipitating events

Diagnosis	Patient Number	Precipitating Event	Time to Attacks
SUNCT	10	glass bottle injury to ipsilateral side of face	7 days
	52	fall onto face	1 day
	17	ipsilateral dental root canal work	3 weeks
	6	extreme stress- death of husband	weeks
	42	fall from a horse onto back	same day
	56	viral infection on return from Europe	2 weeks
	21	withdrew analgesia for shoulder pain	weeks
SUNA	1	flight from Turkey to the UK	2 weeks
	26	bilateral trabeculectomy	weeks

Table 5.4
Laterality of attacks in all patients

	SUNCT	SUNA	All
left sided	14 (33%)	6 (67%)	20 (38%)
right sided	20 (47%)	2 (22%)	22 (42%)
left > right	4 (9%)	1 (11%)	5 (10%)
right > left	3 (7%)	0	3 (6%)
left & right equally	1 (2%)	0	1 (2%)
bilateral	1 (2%)	0	1 (2%)
total	43	9	52

5.5 Site of attacks

Eighty-eight per cent of SUNCT and 78 % of SUNA patients had pain in the distribution recognized by the IHC criteria (Headache Classification Committee of The International Headache Society, 2004); that is the eye, retro-orbital region and temple. The majority of SUNCT patients (29, 67 %) experienced pain in the eye, with 24 (56 %) having retro-orbital pain, 16 (37 %) with forehead pain, 16 (37 %) with pain in the nose, and 14 (33 %) each in the temple and maxillary (second) division of the trigeminal nerve. Twelve had pain in the back of the head, nine had pain in the top of the head, nine in the teeth, four had pain in the side of the head, three in the eyebrow, and two in the ear. One patient had pain in the neck. In contrast, only two SUNA patients (22 %) had pain in the eye. The pain was in the retro-orbital region in five patients (56 %) and temple in five patients (56 %). Four patients (44 %) had pain in the side of the head. There was pain in the second (maxillary) and third (mandibular) division of the trigeminal nerve in one patient each. Two further patients with SUNA (#59 and #43) had pain in both V_2 and V_3 . Two patients had pain in the teeth, two in the back of the head, and one each in the neck, ear and forehead (Table 5.5).

Table 5.5

Site of attacks

	SUNCT	SUNA
eye	29 (67%)	2 (22%)
retro-orbital region	24 (56%)	5 (56%)
eyebrow	3 (7%)	0 (0%)
forehead	16 (37%)	1 (11%)
temple	14 (33%)	5 (56%)
side head	4 (9%)	4(44%)
top head	9 (21%)	0 (0%)
back head	12 (28%)	2 (22%)
nose	16 (37%)	1 (11%)
V ₂	14 (33%)	3 (33%)
V ₃	0 (0%)	3 (33%)
teeth	9 (21%)	2 (22%)
neck	1 (2%)	1 (11%)
ear	2 (5%)	1 (11%)

Table 5.6

Associated autonomic symptoms

	SUNCT	SUNA	CH*
conjunctival injection (CI)	43 (100%)	2 (22%)	77
lacrimation	43 (100%)	3 ipsilateral, 1 contralateral (44%)	91
both CI and lacrimation	43 (100%)	0 (0%)	
nasal blockage	17 (40%)	2 (22%)	75
rhinorrhoea	23 (53%)	2 (22%)	72
eyelid oedema	21 (49%)	1 (11%)	74
ptosis	22 (51%)	3 (33%)	74
facial flushing	2 unilateral, 2 bilateral (9%)	1 (11%)	
sweating	2 unilateral, 1 bilateral (7%)	1 bilateral (11%)	
other	4 (9%)	3 (33%)	

* After Bahra et al (Bahra et al., 2002)

5.6 Autonomic Symptoms

All of the SUNCT patients had both ipsilateral conjunctival injection and lacrimation associated with their attacks, by definition (Headache Classification Committee of The International Headache Society, 2004). Twenty-two patients (51 %) had ipsilateral ptosis, 17 (40 %) had nasal blockage and 23 (53 %) had ipsilateral rhinorrhoea associated with their attacks. Twenty-one patients (49 %) noticed ipsilateral eyelid oedema, four (9 %) had facial flushing, two of which were unilateral and two bilateral. Three (7 %) had facial sweating, two of which were unilateral and two bilateral. A further four (9 %) had other cranial autonomic symptoms, such as blotchy skin in the face and neck, ipsilateral gritty eye (after Newman (Goadsby and Lipton, 1997; Newman et al., 1994)), ipsilateral cheek oedema, and a sense of ipsilateral aural fullness. The ipsilateral cheek oedema was in a patient whose pain affected both the first (ophthalmic) and second (maxillary) divisions of the trigeminal nerve (#17). One patient also experienced her autonomic symptoms even without the attacks (#57).

Of the nine SUNA patients, two (22 %) had ipsilateral conjunctival injection and four (44 %) had lacrimation. Of those with lacrimation, three were ipsilateral and one was contralateral. None had both conjunctival injection and lacrimation. Two patients (22 %) had both nasal blockage and rhinorrhoea. Three patients (33 %) had ipsilateral ptosis, one (11 %) had ipsilateral eyelid oedema, and one (11 %) had bilateral facial sweating. Three patients (33 %) had other symptoms including visual blurring in the ipsilateral eye, ipsilateral mydriasis, and a feeling of flushing red hot ipsilateral ear in one patient each (Table 5.6). The diagnosis of ‘red ear syndrome’ (Lance, 1996) was considered but discounted by the history.

Association between site of pain and autonomic symptoms

Thirty patients with SUNCT had attacks affecting the second division of the trigeminal nerve (V₂) (cheek and nose). Of these 30 patients, 17 (73 %) had associated nasal autonomic symptoms. There were only eight patients who had V₂ pain but no nasal autonomic symptoms.

Of the four SUNA patients who had V_2 and V_3 pain, two had nasal autonomic symptoms. One patient (#59) specifically reported lacrimation when his pain was predominantly in V_2 and nasal congestion when his pain was predominantly in V_3 .

5.7 Type of pain

Thirty-two of the fifty-two patients (62 %) described their attacks as stabbing. Ten (19 %) had electric-shock type attacks, nine (17 %) described theirs as sharp and eight (15 %) as shooting. Five patients (10 %) described their attacks as burning, five as throbbing and four (8 %) as a pressure. Three patients said their attacks had a boring quality (6 %), and a further three patients (6 %) described needle-like sensations. Two patients (4 %) described the pain as hot, and two patients said they experienced jabs of pain. There was one description each of the following characteristics of the pain: burning, bursting, metallic, scrape, squeeze, sting, tight, twang and twitching (Table 5.7).

5.8 Severity of pain

The patients were asked to rate the severity of their attacks on a verbal rating scale (VRS) of 0 to 10, 0 being no pain at all, and 10 being the most severe pain imaginable. The majority of SUNCT patients (36 patients, 84 %) rated their most painful attacks at 10/10 on the VRS. The range of severity was from 5-10/10, and the range of their most painful attacks was 6-10/10. The median was 10.

In contrast, out of the nine patients with SUNA, only three patients (33 %) recorded their maximum severity as 10/10. A further three patients recorded their maximum severity as 9/10. The range of severity was 5-10/10 and the median was 9 (Table 5.8).

Out of the SUNCT patients, most said that this was the most painful condition they had ever experienced. None could name a pain which they had experienced which was more painful than their SUNCT attacks. Specifically, patients said that their attacks were worse

than childbirth in six patients, tooth abscesses and associated pains in two patients, and gallstones, fractured ribs, renal stones and other headaches in one patient each. For SUNA patients eight had not experienced pain greater than their SUNA attacks. Specifically, the pain was described as worse than childbirth and appendicitis in one patient each. Only one patient cited the pain of bilateral trabeculectomies as greater than the pain of her SUNA attacks.

Table 5.7
Characteristics of pain

Type of attack	SUNCT	SUNA	All
stab	29 (67%)	3 (33%)	32 (62%)
electric shock	9 (21%)	1 (11%)	10 (19%)
sharp	7 (16%)	2 (22%)	9 (17%)
shooting	7 (16%)	1 (11%)	8 (15%)
burn	5 (12%)	0 (0%)	5 (10%)
throb	3 (7%)	2 (22%)	5 (10%)
pressure	3 (7%)	1 (11%)	4 (8%)
needle	3 (7%)	0 (0%)	3 (6%)
boring	2 (5%)	1 (11%)	3 (6%)
jab	2 (5%)	0 (0%)	2 (4%)
hot	1 (2%)	1 (11%)	2 (4%)
burning	1 (2%)	0 (0%)	1 (2%)
burst	1 (2%)	0 (0%)	1 (2%)
scraping	1 (2%)	0 (0%)	1 (2%)
squeeze	1 (2%)	0 (0%)	1 (2%)
sting	1 (2%)	0 (0%)	1 (2%)
tight	1 (2%)	0 (0%)	1 (2%)
twang	0 (0%)	1 (11%)	1 (2%)
twitching	0 (0%)	1 (11%)	1 (2%)
metallic	0 (0%)	1 (11%)	1 (2%)

Table 5.8
Severity of pain

	SUNCT	SUNA
no of patients	43	9
patients with attacks 10/10	36 (84%)	3 (33%)
range of severity (VRS)	5 to 10/10	5 to 10/10
mean	9.7	8.9
median	10	9
patients with pain worse	0	1 (trabeculectomy)

5.9 Other symptoms

Agitation

Of the 43 SUNCT patients, there was data on 40 patients as to whether they felt agitated during the attack. Twenty-five patients (62 %) were agitated during an attack, with five patients with SUNA (55 %) having agitation. Agitation has been reported in 88 % of patients with cluster headache (Torelli and Manzoni, 2003), and in 50% of patients with paroxysmal hemicrania (Antonaci and Sjaastad, 1989; Cohen et al., 2006), but is less of a feature in migraine, where movement classically makes the pain worse (Headache Classification Committee of The International Headache Society, 2004). Of the 30 agitated patients, 11 of them (37 %) had migraine. Of the nine patients in whom movement made the pain worse, six of them (67 %) had migraine, and of the remaining three patients, one had a family history of migraine (Figure 5.1).

Migrainous symptoms

Photophobia and phonophobia are also generally associated with migraine, although usually this is bilateral. Unilateral photophobia and phonophobia can occur in migraine (Drummond, 1986; Vingen et al., 1998a), cluster headache (Vingen et al., 1998b) and has also been reported in paroxysmal hemicrania (Irimia et al., 2005). In this group, 21 SUNCT patients (49 %) and six SUNA patients (67 %) had migrainous biology: a personal or family history of migraine. Twenty-two SUNCT patients experienced photophobia or phonophobia, and of these 12 were patients with migrainous biology. Three SUNA patients experienced photophobia or phonophobia, and of these two had migrainous biology. Of the four SUNCT patients with a combination of nausea, photophobia and phonophobia, all had migrainous biology (Figure 5.2).

Sixteen SUNCT patients had photophobia, and of these eleven had photophobia ipsilateral to the pain (69 %). Two SUNA patients had photophobia, both ipsilateral to the pain. Thirteen SUNCT patients had phonophobia, with four (31 %) ipsilateral to the pain. Two SUNA patients had phonophobia, both ipsilateral to the pain (Table 5.9).

Figure 5.1
Agitation or restlessness during attacks of SUNCT/SUNA

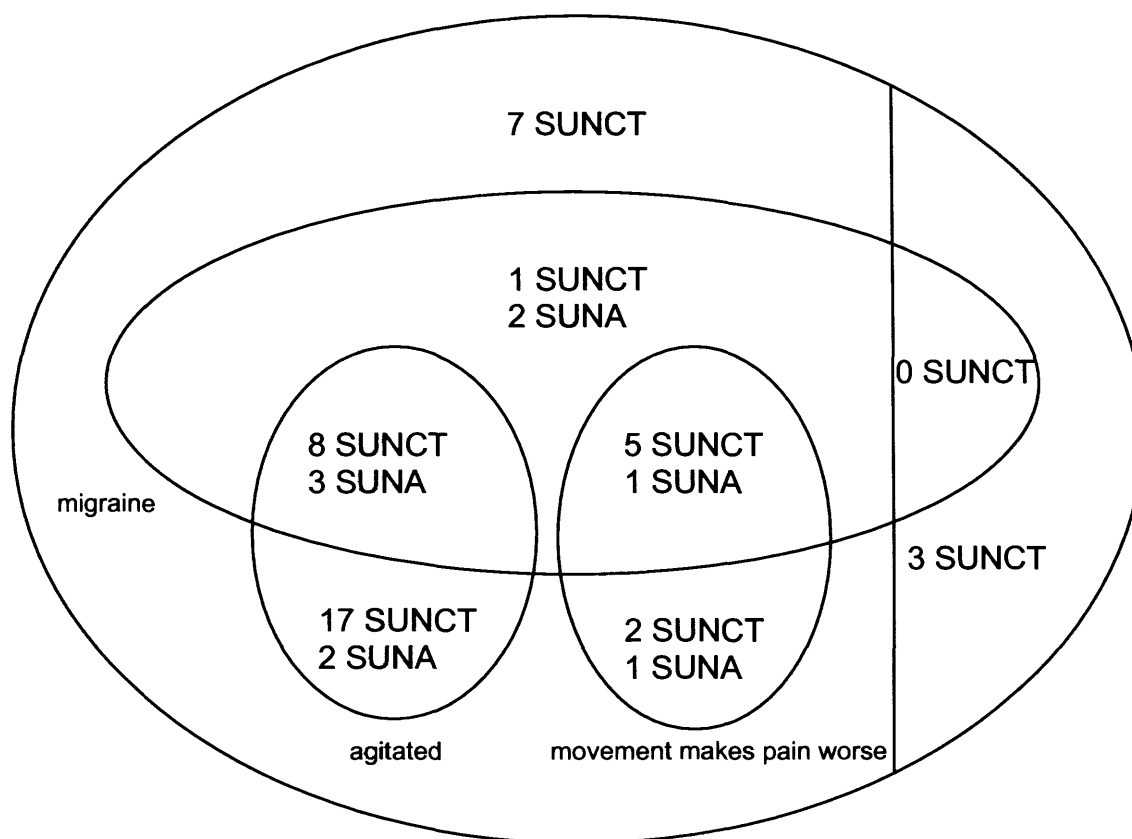
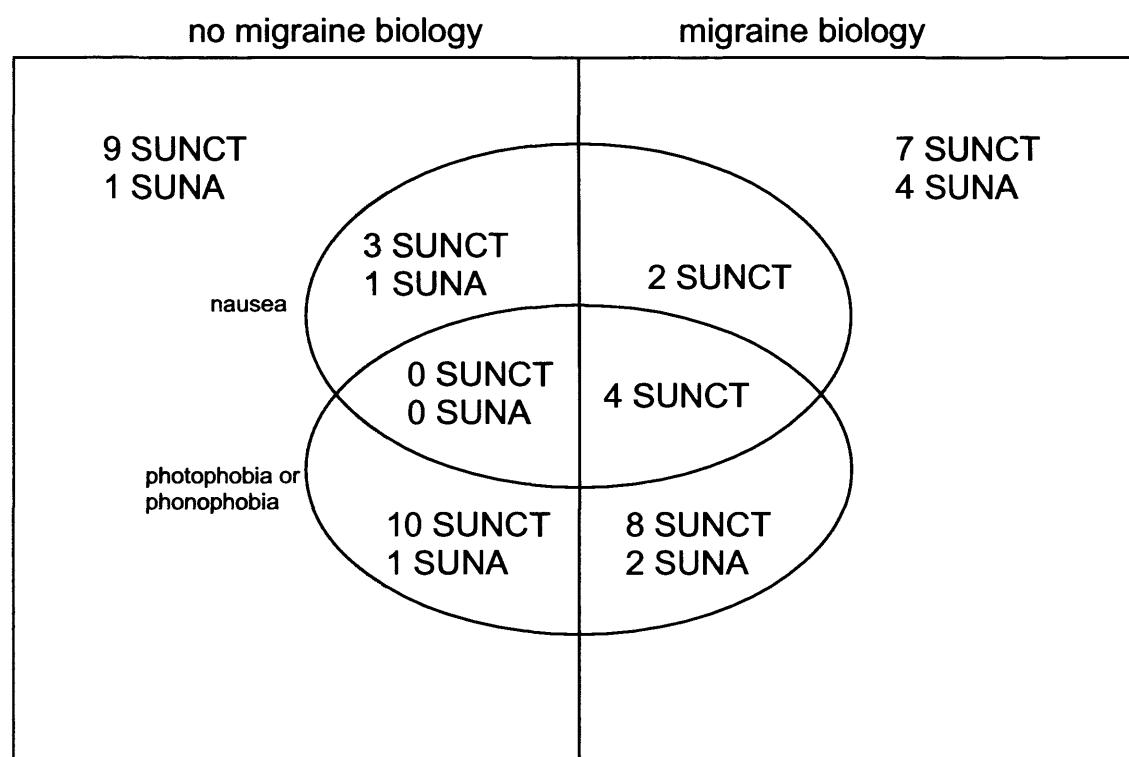


Figure 5.2

Photophobia and phonophobia in SUNCT/SUNA

**Table 5.9**

Laterality of photophobia and phonophobia

	SUNCT	SUNA	SUNCT and SUNA
Total photophobia	16 (37%)	2 (22%)	18 (35%)
unilateral photophobia	11 (26%)	2 (22%)	13 (25%)
Total phonophobia	13 (30%)	2 (22%)	15 (29%)
unilateral phonophobia	4 (9%)	2 (22%)	6 (12%)

The vast majority of patients in this cohort had no symptoms of aura such as visual, speech or sensory disturbances (Headache Classification Committee of The International Headache Society, 2004), nor any motor disturbance associated with their attacks. One patient (#56) had some dizziness with his attacks. The SUNA patient (#SUNA44) with visual blurring only in the ipsilateral eye, and only for the duration of the attack, was not considered to have aura.

5.10 Character, duration and frequency of attacks

Attacks took one or more of three forms: single stabs, a group of stabs or a long attack with a 'saw-tooth' pattern of stabs between which the pain would not return to the baseline (Figure 5.3).

Of the SUNCT patients, 15 had single attacks only, two had groups of stabs only (of whom one had groups of groups- #21), and eight had saw-tooth attacks only. Nine patients had single attacks and groups of stabs, five patients had single attacks and saw tooth attacks, and one patient had groups of stabs and saw tooth attacks. Three patients had all three types of attacks. In the SUNA patients, three patients had single attacks only, two patients had groups of stabs only, and one had saw tooth attacks only. Two patients had single attacks and groups of stabs, and one had single attacks plus saw tooth attacks (Figure 5.4).

Figure 5.3

The three types of clinical picture of attacks of SUNCT/SUNA

Pain (Verbal Rating Scale from 0 to 10)

1. Single stabs

2. Each attack is a group of stabs

3. Saw-tooth pattern

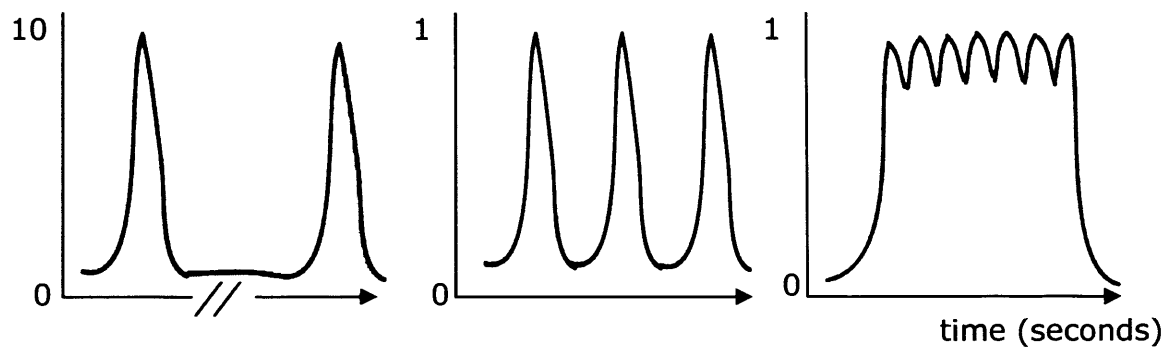
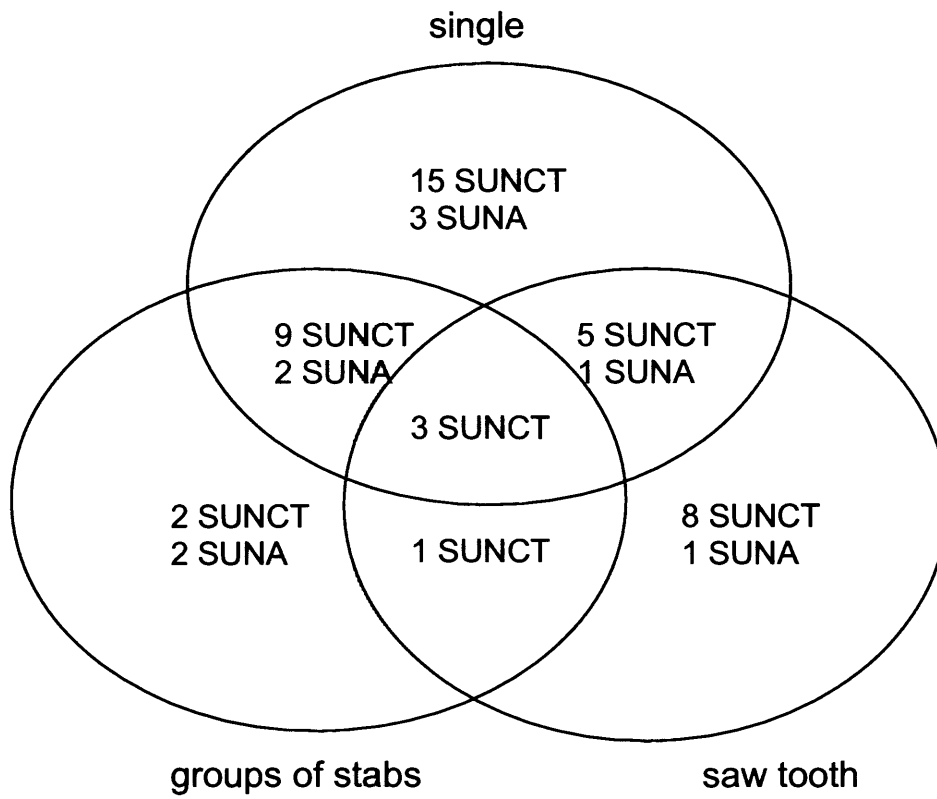


Figure 5.4

Distribution of types of attacks illustrated in Figure 5.3 by condition



5.11 Attack timing

Length of attacks

The International Headache Society criteria for the length of attacks is 5-240 seconds (Headache Classification Committee of The International Headache Society, 2004). However patients may have groups of attacks for which each individual stab is of the order of 5-240 seconds, but the attacks themselves are perceived as much longer in the order of minutes or even hours. This may have caused some diagnostic confusion in the past, as patients with attacks lasting more than 240 seconds may have had the diagnosis of SUNCT or SUNA falsely ruled out, whereas in fact their individual attacks were much shorter. In this study, the length of the individual stab attacks is reported in addition to the duration of groups of stabs or saw tooth attacks.

For all patients, the range of length of stab attacks was 1-600 seconds, with a mean length of 58 seconds and median 10 seconds. This included the stabs which came as part of a group of stabs, or as part of the saw-tooth attacks. The groups of stabs ranged in length between 10 and 1200 seconds, with a mean of 396 seconds and median of 300 seconds. The saw tooth attacks ranged from 5 to 12000 seconds (200 minutes), with a mean of 1160 seconds and median 285 seconds. One patient (#21) had stabs lasting one second each, which would come in groups of 10 seconds, which in turn would occur in groups of groups, lasting 3600 seconds at a time. One patient (#51) had attacks which lasted as long as the trigger lasted; for instance pulling his hair for one second or one hour would result in an attack lasting one second or one hour, respectively. This patient's data was not included in the analysis of length of attacks. The rest of the results are in Table 5.10.

Table 5.10

Length of attacks and number of attacks per day, and attack load in minutes per day

attack length	single stab	stab groups	saw tooth	number of attacks/day	attack load per day
mean	58 sec	396 sec	1160 sec	59	139 min
median	10 sec	300 sec	285 sec	20	47 min
range	1-600 sec	10-1200sec	5-12000 sec	2-600/day	2-1350 min

Number of attacks per day

The International Headache Society criteria for the number of attacks a day is 20-300 (Headache Classification Committee of The International Headache Society, 2004).

However 10 patients, of whom 8 had SUNCT and 2 had SUNA, had so many attacks a day that they could not accurately quantify them. The number of attacks ranged from 2 to 'many hundreds'. In total, 42 of the 52 patients were able to quantify their attacks. The number of attacks per day ranged from 2 to 600, with a mean of 59 attacks per day and median of 20 attacks per day.

Some patients had longer attacks than others, and some had groups of attacks. For instance one patient (#30) had stabs lasting 120 seconds which would occur 12 times per hour, for 3 hours at a time, and she would get 3 of these attacks a day. This could either be reported as 3 attacks, or as 108 attacks a day. It would therefore make sense to report both the number of attacks per day and the attack load per day, which would be the number of minutes of pain per day. This may better marker for monitoring the therapeutic response to treatments; the results are illustrated in Table 5.10.

Diurnal Variation of Attacks

Thirty-seven of the forty-three SUNCT patients and eight of nine SUNA patients could specify whether their attacks occurred more during waking or sleeping hours. In three patients (7 %) with SUNCT their attacks occurred primarily during sleep. Seventeen patients (40 %) experienced attacks mainly during waking hours, and 17 patients (40 %) experienced attacks equally during sleep and wakefulness. Attacks were specifically worse in the early morning in four patients. Four patients with SUNA had attacks mainly during waking hours, with one especially in the early mornings, and four experienced attacks both during sleep and wakefulness (Table 5.11).

Table 5.11

Diurnal variation of attacks

	SUNCT	SUNA	total
awake (early morning)	17 (3) (40%)	4 (1) (44%)	21
asleep	3 (7%)	0	3
both	17 (1) (40%)	4 (44%)	21
unspecified	6	1	7

5.12 Triggering of Attacks

In the SUNCT patients, one patient (#51) only had triggered attacks with no spontaneous ones. Twelve patients (28 %) said that most of their attacks were triggered, seven had equal numbers of triggered and spontaneous attacks, 12 (28 %) had more spontaneous than triggered attacks, and six (14 %) had entirely spontaneous attacks with no triggers. In contrast, in the SUNA patients, two (22 %) had mostly triggered attacks, and six (67 %) had entirely spontaneous attacks with no triggers.

In thirty-four SUNCT patients (79%) and three SUNA patients (33%), the attacks could be triggered by various cutaneous stimuli. Touching the face was a trigger in 27 SUNCT patients. This was the ipsilateral first division of the trigeminal nerve in six patients, ipsilateral second division of the trigeminal nerve in seven patients, ipsilateral side of the face in both divisions or unspecified area in 13 patients, and bilateral first division in one patient (#47) with strictly unilateral attacks. Other triggers included chewing or eating, wind on the face, washing the face, brushing teeth, movement of the head or jaw, talking, washing or brushing the hair, exercise, light on the face, showering, shaving, blowing the nose; and smoke, strong smells, and a warm environment. Alcohol was a trigger in one SUNA patient (#40) in that it would trigger attacks of ptosis. Other trigger factors included dental work, lifting heavy objects, blinking, stretching of the skin on the ipsilateral side of the face, and licking the lips on the ipsilateral side in one SUNCT patient each. Lying on the ipsilateral side was a trigger to attacks in one SUNA patient.

Factors making the attacks worse, by increasing the frequency or severity of attacks, included stress in three SUNCT and one SUNA patients, travel across time zones in three SUNCT patients, tiredness in one SUNCT and one SUNA patients, and bad weather in one SUNCT patient.

When asked about a refractory period between attacks, only two of the SUNCT patients (5 %) and one SUNA patient (11 %) had a refractory period; that is, 95 % of SUNCT patients and 89 % of SUNA patients could have one attack triggered or occurring spontaneously immediately after cessation of another one (Table 5.12).

Table 5.12

Triggered attacks and refractory period

Triggers to attacks	SUNCT	SUNA	total
touch	27 (63%)	0 (0%)	27 (52%)
chew/eat	26 (60%)	2 (22%)	28 (54%)
wind	17 (40%)	1 (11%)	18 (35%)
wash face	17 (40%)	0 (0%)	17 (33%)
brushing teeth	16 (37%)	0 (0%)	16 (31%)
move	14 (33%)	2 (22%)	16 (31%)
talk	9 (21%)	1 (11%)	10 (19%)
wash or brush hair	5 (12%)	0 (0%)	5 (10%)
exercise	5 (12%)	1 (11%)	6 (12%)
light	4 (9%)	0 (0%)	4 (8%)
shower	4 (9%)	0 (0%)	4 (8%)
shaving	4 (9%)	0 (0%)	4 (8%)
blow nose	3 (7%)	0 (0%)	3 (6%)
alcohol	0 (0%)	1 (11%)	1 (2%)
smoke	1 (2%)	0 (0%)	1 (2%)
smells	1 (2%)	0 (0%)	1 (2%)
warm	1 (2%)	0 (0%)	1 (2%)
others	5 (12%)	0 (0%)	5 (10%)
Factors making attacks worse			
stress	3 (7%)	1 (11%)	4 (8%)
tired	1 (2%)	1 (11%)	2 (4%)
travel	3 (7%)	0 (0%)	3 (6%)
weather	1 (2%)	0 (0%)	1 (2%)
all triggered	1 (2%)	0 (0%)	1 (2%)
mostly triggered	12 (28%)	2 (22%)	14 (27%)
equal triggered and spontaneous	7 (16%)	0 (0%)	7 (13%)
mostly spontaneous	12 (28%)	0 (0%)	12 (23%)
all spontaneous	6 (14%)	6 (67%)	12 (23%)
unknown	5 (12%)	1 (11%)	6 (12%)
refractory period	3 (5%)	1 (11%)	4 (8%)

5.13 Background Pain, Migraine and Analgesic Overuse

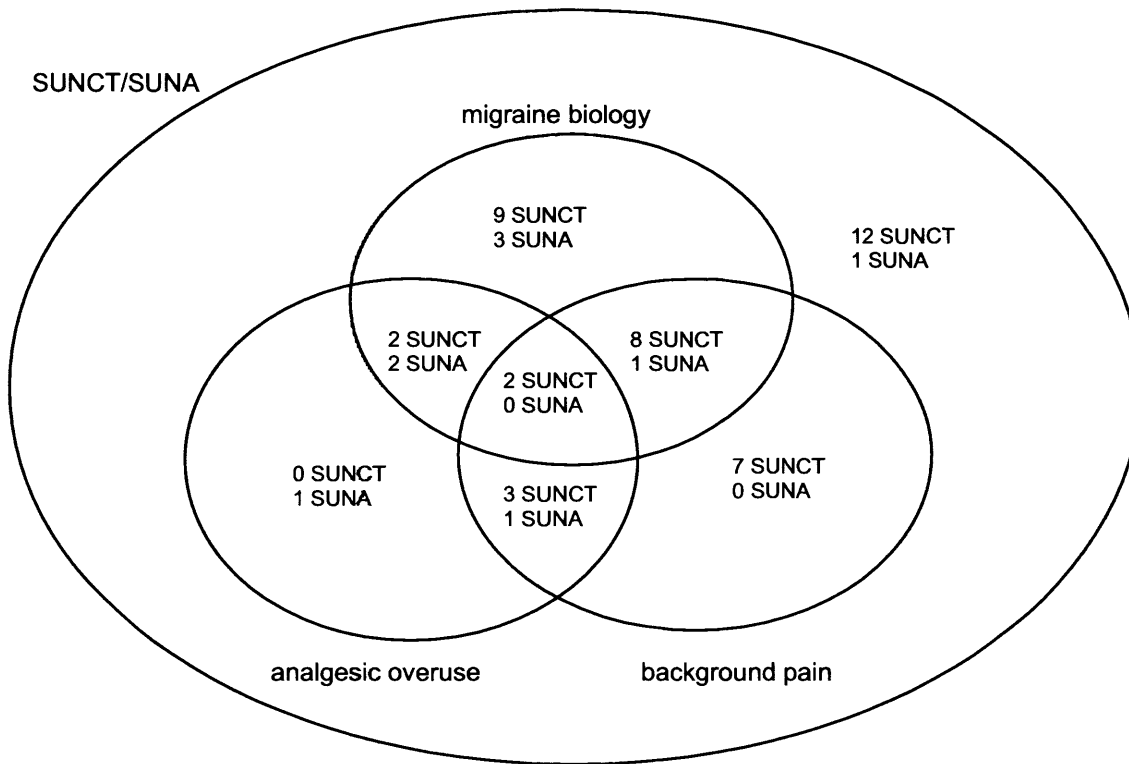
Classically SUNCT and SUNA are not associated with background pain. This study identified 20 patients with SUNCT and two patients with SUNA who had interictal background pain. Initially some of these patients were misdiagnosed as having hemicrania continua, but negative placebo-controlled Indomethacin tests ruled this out as a diagnosis (see Table 7.4).

Fifteen SUNCT patients (35 %) had a personal history of migraine, and in total 21 (49 %) had migrainous biology, that is, a personal history of migraine or a family history of migraine in a first- degree relative. Six SUNA (67 %) patients had migraine, and all had a family history of migraine. The relationship between migrainous biology and SUNCT/SUNA was assessed, and found in total 40 % of patients had a personal history of migraine and 52 % had migrainous biology.

Analgesic overuse, defined as the use of analgesics on 15 or more days per month, was present at some point in seven SUNCT patients and four SUNA patients. The analgesics used were codeine, paracetamol, dihydrocodeine, codeine and paracetamol combinations in most patients, and codeine and morphine in one patient (#52). Of these 11 patients, six had migrainous biology. Analgesic overuse is known to lead to chronic daily headache, especially in migraine patients (Bahra et al., 2003), and it was found that two SUNCT patients with migrainous biology and analgesic overuse developed a chronic daily headache. However even without analgesic overuse, there was background pain present in 15 SUNCT patients and one SUNA patient, of whom nine had migrainous biology. These interactions are illustrated in Figure 5.5.

Figure 5.5 SUNCT/SUNA

Migraine biology, analgesic overuse and background headache



5.14 Periodicity and Chronicity of SUNCT and SUNA

All the SUNA patients had primary chronic SUNA; that is attacks occurring for a year or more without more than a month's break. One patient (#24) went into spontaneous remission after 1 year and had been pain free for 2½ years at the time of interview.

Thirteen SUNCT patients (30 %) had primary episodic SUNCT. Their bouts lasted for a mean 7.5 weeks (range 1-30 weeks and median 4 weeks). The average remission time was 52 weeks, with a range of 3-364 weeks (7 years) and a median of 26 weeks.

Seventeen SUNCT patients had primary chronic SUNCT (40 %). Ten patients (23 %) had secondary chronic SUNCT, with average time from the start of the disease to chronic SUNCT being 8.4 years (range 1-16 years, median 8.5 years).

One SUNCT patient (#3) and one SUNA patient (#SUNA24) had primary chronic forms of the syndromes for more than a year, and then went into remission for 2 years and 3 years, respectively. One SUNCT patient (#49) had primary chronic SUNCT for 2 years, then went into remission for 14 years, then had secondary episodic SUNCT with a bout lasting 8 months and remission to date. One patient (#14), had primary chronic SUNCT which went into remission for a year and then the patient was lost to follow-up (Table 5.13).

Table 5.13
Periodicity and Chronicity of SUNCT and SUNA

	SUNCT	SUNA	SUNCT & SUNA
primary episodic	13 (30%)	0 (0%)	13 (25%)
primary chronic	17 (40%)	8 (89%)	25 (48%)
primary chronic plus remission	2 (5%)	1 (11%)	3 (6%)
secondary chronic	10 (23%)	0 (0%)	10 (19%)
secondary episodic	1 (2%)	0 (0%)	1 (2%)
comments			
episodic SUNCT	bouts mean 7.5 weeks, range 1-30 weeks, median 4 weeks		
	remissions mean 51.6 weeks, range 3-364 weeks, median 26 weeks		
secondary chronic SUNCT	time to chronicity 8.4 years, range 1-16 years, median 8.5 years		

5.15 SUNCT and SUNA with abnormal examination and MRI findings- *symptomatic SUNCT and SUNA*

Thirteen SUNCT patients (30 %) and one SUNA patient (11 %) had abnormal findings on neurological examination. These were mainly ipsilateral sensory changes, either reduced sensation to pinprick in V₁ or V₂ (five SUNCT (12 %) and one SUNA patient (11%)) or hyperaesthesia to pinprick in V₁ (one SUNCT (2%)). One SUNCT patient had ipsilateral reduced sensation in V₂ secondary to an infraorbital nerve block. Six SUNCT patients (14%) had other abnormal signs; one had a mildly abnormal response to pinprick on the ipsilateral side of the body (#27), and one with a Horner's syndrome, which was investigated and no cause was found (#23). The remaining three patients had signs relating to other pathology, which were: reduced field of vision in one eye in a patient with microprolactinoma (#25), ipsilateral VI and contralateral XII nerve palsy after a head injury (#51), and contralateral pyramidal weakness following surgery to remove astrocytoma (#57).

Thirty-six SUNCT and eight SUNA patients had results of cranial imaging, which in the majority of cases was MRI. Nineteen SUNCT patients (44%) and seven SUNA patients (78%) had normal intracranial appearances. Of the remainder, five SUNCT patients had incidental findings, such as scattered cerebral white matter lesions consistent with age-related infarctions.

Twelve SUNCT and one SUNA patient had abnormal intracranial findings. These were:

- 1) Vascular loops compressing on the trigeminal nerve in one patient. One was ipsilateral to the pain (#13), one had bilateral loops but only unilateral pain (#46), and one had a loop on one side but had bilateral attacks (#55).
- 2) Pathological white matter changes in two SUNCT patients and one SUNA patient. One SUNCT patient had scattered cerebral white matter lesions (#7 reported in (Matharu et al., 2004b) and one with a lesion on the ipsilateral cerebral peduncle (#52). The SUNA patient had primary progressive multiple sclerosis with

extensive white matter changes and lesions in the midbrain, pons and middle cerebral peduncle (#SUNA4).

- 3) Pituitary lesions in three SUNCT patients, of whom two had macroadenomas (#37 reported in (Matharu et al., 2003c) and #20), which resolved on treatment of the macroadenoma; and one had a microprolactinoma (#25), the excision of which rendered her pain free for 8 months.
- 4) Space occupying lesions in two patients, which included a parietal astrocytoma in one patient (#57), which on excision did not cause a resolution of her SUNCT. The other patient (#51) had an ipsilateral parieto-occipital lesion with meningeal inflammation of unknown cause, which had been excised two years before the onset of his SUNCT. This patient had also suffered a head injury and was left with a residual ipsilateral VI nerve and contralateral XII nerve palsy (Table 5.14).

Table 5.14

Secondary SUNCT/ SUNA and abnormal intracranial imaging

	SUNCT	SUNA	all
Abnormal examination:			
ipsilateral reduced sensation to pinprick	5 (12%)	1 (11%)	6 (12%)
ipsilateral hyperaesthesia	1 (2%)	0 (0%)	1 (2%)
ipsilateral changes post procedures	1 (2%)	0 (0%)	1 (2%)
other neurological abnormalities	6 (14%)	0 (0%)	6 (12%)
Intracranial imaging:			
total number imaged	37	8	45
normal intracranial appearances	20 (54%)	7 (88%)	27 (60%)
incidental findings	6 (16%)	0 (0%)	6 (13%)
abnormal intracranial appearances:			
vascular loops	3 (8%)	0 (0%)	3 (7%)
pathological white matter changes	2 (5%)	1 (12%)	3 (7%)
pituitary lesions	3 (8%)	0 (0%)	3 (7%)
space occupying lesions	2 (5%)	0 (0%)	2 (4%)
unusual configuration in brainstem and lacune in thalamus	1 (3%)	0 (0%)	1 (2%)
total abnormal intracranial appearances	11 (29%)	1 (12%)	12 (27%)

Chapter 6

Discussion: Clinical Study of Phenotype of SUNCT and SUNA

This study reports the first substantial case series clinically characterising SUNCT/SUNA. The syndrome fundamentally is of unilateral, episodic severe pain that occurs in stabs or jabs and is associated with ipsilateral cranial autonomic outflow. The attacks are more severe than has hitherto been reported; they can be prolonged, and are triggerable without an apparent refractory period in the vast majority. The series clearly establishes the existence of what has been called SUNA, and provides a basis for considering the two syndromes as closely related, with the majority having SUNCT. The data suggest the need for changes in the International Headache Society classification and provide a firm basis for neurologists to recognize this relatively newly identified, highly disabling form of primary headache.

6.1 Epidemiology

The prevalence of SUNCT is unknown, although the low number of hitherto reported cases suggests that it is very rare. The fact that at the National Hospital for Neurology and Neurosurgery there are only 52 SUNCT and SUNA cases referred in the UK with a population of 59.6 million (www.statistics.gov.uk) may highlight the rarity of the syndrome. Moreover, since we have seen in excess of 600 patients with trigeminal autonomic cephalgias over the same period, this is a small group. However, the fact that the majority of the patients had previous diagnoses before they were diagnosed with SUNCT or SUNA (Table 5.2) suggests that there may be more cases of SUNCT and SUNA which have been misdiagnosed.

6.2 Male:female ratio

SUNCT has been thought to have a male preponderance, with a recent review giving a male:female ratio of 1.3:1 (28 males and 22 females) (Matharu et al., 2003a). This study

finds a slightly higher ratio of 1.5:1 for total SUNCT and SUNA combined. However, when separated into SUNCT and SUNA, there is a higher male:female ratio in SUNCT (2:1), and almost the opposite ratio in SUNA (0.5:1). Thus it could be that the full syndrome of SUNCT with both conjunctival injection and tearing is commoner in men than in women, with SUNA being commoner in women than men. Alternatively the sample number for SUNA (9 patients) may be too small to make a significant comment.

6.3 Site of Pain

The International Headache Society describes the site of pain in SUNCT as unilateral orbital, supraorbital or temporal pain (Headache Classification Committee of The International Headache Society, 2004). In our series, the majority of SUNCT patients conformed to these criteria (78%), with orbital (67 %), supraorbital/forehead (37 %), or temporal (33 %) pain, the latter of which was present in 56 % of SUNA patients. However, 56 % of both SUNCT and SUNA patients reported retro-orbital pain, and the pain was reported in wider areas of the head and face, including the top, side and back of head, nose, second and third divisions of the trigeminal nerve, teeth, neck and ear. It is interesting to note that only a small proportion of SUNA patients had pain in the eye, supraorbital region or forehead, but pain was more likely to be reported in the temple. Three patients with SUNA (33 %) had pain which radiated to the third (mandibular) division of the trigeminal nerve, whereas no SUNCT patients had pain in V₃. This may illustrate a difference between the two syndromes, such that SUNCT is more likely to affect the orbital and supraorbital regions, and SUNA is more likely to affect the temple and V₂ and V₃.

6.4 Laterality of Attacks

Attacks of SUNCT and SUNA have been typically described as strictly unilateral and side-locked (88 %), with a slight preponderance of SUNCT attacks on the right (Matharu et al., 2003a). In this series 80% of patients had side-locked attacks. Side-alternating attacks are documented in 20 % of SUNCT patients, which have been observed in a few

cases previously (D'Andrea and Granella, 2001; D'Andrea et al., 2001; Matharu et al., 2004b). One patient reported attacks which affected both sides simultaneously (#55). This is considered atypical of SUNCT but has been reported before (Pareja and Sjaastad, 1997; Sabatowski et al., 2001). In that patient's case a vascular loop was noticed on MRI on the right side only, even though his pain was bilateral. Conversely another patient (#46) had bilateral vascular loops impinging on the brainstem, but only suffered attacks on the right side. It seems that a pathogenetic role of vascular loops compressing the brainstem or trigeminal nerve may not be as important in SUNCT as in trigeminal neuralgia (Goadsby et al., 2001).

6.5 Severity of Pain

The pain of SUNCT and SUNA is usually excruciating, on a verbal rating scale of 10/10 in severity. This serves to highlight the devastating morbidity of these syndromes, especially with a mean time to diagnosis of 6.7 years in SUNCT and 7.1 years in SUNA (Table 5.2), and subsequent failure of response to conventional medications (Pareja et al., 1995).

6.6 Duration, Frequency and Temporal Profile of Individual Attacks

The International Headache Classification specifies attack length of 5-240 seconds, with 3 to 200 attacks per day. These results demonstrate that attacks may take on different characters; single stabs, groups of stabs, or a longer attack comprised of many stabs between which the pain does not resolve to normal, thus giving a 'saw-tooth' phenomenon (Figure 5.3). Although this variability in the character of attacks is well recognised in the literature (Antonaci and Sjaastad, 1989), it may have led to confusion in the description of length of attacks.

The length of single stabs, whether alone, as part of a group, or as part of a saw-tooth attack, ranged from 1-600 seconds with a mean of 56 seconds. This correlates reasonably well with the IHS classification of length of attacks. The shorter stabs (1-5 seconds in length) may make up part of a group of stabs or a saw-tooth attack which will last longer

in total. Groups of stabs, or saw-tooth attacks may be made up of many individual stab attacks, thus a 'single attack' would be perceived as longer than 240 seconds leading to wrong diagnoses of paroxysmal hemicrania or cluster headache, since they have longer attacks at 2-30 minutes and 15-180 minutes respectively (Headache Classification Committee of The International Headache Society, 2004).

Another consideration in assessing the temporal profile of attacks is the wide inter-patient variation in the number of attacks per day, and the length of these attacks. For example, a patient with 200 attacks a day, each lasting 2 seconds, will have a rather different experience from the patient with 3 saw-tooth attacks a day, lasting up to thirty minutes at a time. The first patient will have 400 seconds of pain a day, which is just less than 7 minutes. The second patient will have 180 minutes of pain a day. From a therapeutic point of view it would be desirable to reduce both the number of attacks per day, but also the attack load; that is the number of minutes of pain per day. A system of quantifying SUNCT and SUNA attacks is hereby proposed, in the following terms for the purpose of therapeutic studies:

- 1) type of attack (stab, group or saw-tooth)
- 2) number of attacks per day
- 3) attack load in minutes per day

6.7 Frequency and Periodicity of Attacks

Most cases of SUNCT in the literature have occurred in an episodic manner, with the symptomatic bouts alternating with remissions in an erratic manner. In a series of 21 patients, the symptomatic bouts last from a few days to several months and occurred once to twice annually, although a maximum of 22 episodes per year have been reported, and the symptomatic periods appeared to increase in frequency and duration over time (Pareja and Sjaastad, 1997). Remissions typically lasted for a few months, but have been reported to last from 1 week to 8.5 years (Jimenez-Huete et al., 2002). Both the episodic and chronic forms of SUNCT have been included in the International Headache Society Classification of Headache (Headache Classification Committee of The International

Headache Society, 2004). In this series only 13% of SUNCT patients and no SUNA patients had the primary episodic form of the disease. Indeed, most of the SUNA patients (89%) had primary chronic disease. Most, SUNCT patients (63%) had either primary chronic or secondary chronic SUNCT. The average time from the start of the syndrome to chronicity was 8.4 years. There also exist one SUNCT and one SUNA patient with primary chronic disease, that is attacks occurring for more than a year without more than a month's remission, who then went into spontaneous remission for 2 and 3 years, respectively. Additionally a patient with 2 years of SUNCT had a spontaneous remission for 14 years, and then had a bout lasting 8 months with remission afterwards (to date).

These data differ from cluster headache databases, where most patients have the primary episodic form of cluster headache (79 %), and a small percentage (8 %) go on to develop secondary chronic CH (Bahra et al., 2002). Chronic cluster headache can revert or evolve to secondary episodic CH in as many as 50% of affected individuals (Manzoni et al., 1991).

The study also highlights differences in the diurnal variation of SUNCT attacks. Only 7 % of SUNCT patients reported predominantly nocturnal attacks as opposed to up to 73 % of CH patients (Bahra et al., 2002; Russell, 1981). However, a further 40 % of SUNCT patients experienced attacks that could occur equally during sleep and wakefulness. This may be due to the fact that SUNCT attacks are triggered by cutaneous stimuli that would occur more often during wakefulness; however the diurnal variation in the attacks was equally diverse between those patients who had predominantly triggered and those with mainly spontaneous attacks.

6.8 Interictal pain

This study describes 20 patients with SUNCT and 2 patients with SUNA who had interictal background pain (Figure 5.5). SUNCT is not usually thought of as having a component of background pain, although a persistent dull interictal ache has been described in association with SUNCT in 2 cases (Matharu et al., 2004b; Pareja et al.,

1996b). The differential diagnosis for what may appear to be prolonged attacks includes paroxysmal hemicrania and cluster headache. For constant interictal pain the differential diagnosis would include hemicrania continua. However there are important clinical characteristics which lead to the suspicion of a diagnosis of SUNCT, such as the cutaneous (or other) triggerability of attacks and the lack of a response to indomethacin. It is helpful to perform a controlled indomethacin test to rule out paroxysmal hemicrania and hemicrania continua (Antonaci et al., 1998).

6.9 Concomitant Headache, Migraine and Background Pain

As seen in Figure 5.5, 34 % of patients had a personal history of migraine and 50% had migrainous biology. This is in contrast to the 15 % migraine prevalence in the general population (Steiner et al., 2003). Migraine is considered to be more common in patients with cluster headache (Bahra et al., 2002), and may coexist with paroxysmal hemicrania (Cohen et al., 2006). The increased prevalence of migraine in this cohort of SUNCT and SUNA patients may reflect a predisposition for primary headache syndromes, or simply that the patients more readily are coming to medical attention because of the SUNCT/SUNA. Patients with primary headache syndromes, notably migraine (Bahra et al., 2003) or cluster headache (Paemeleire et al, 2004) may develop chronic daily headache with analgesic overuse. SUNCT and SUNA patients with migraine biology, especially those who overuse analgesics, may also be at increased risk of developing an interictal chronic background pain.

6.10 Family History

There is only one reported case in the literature of a family history of SUNCT (Gantenbein and Goadsby, 2005). This case is in the current cohort (#12). It is well known that migraine has a significant genetic component (Ferrari, 1998), and this is strengthened by the description of clear genetic mutations in familial hemiplegic migraine (Ophoff et al., 1996). As for the TACs, there have been reports of familial cluster headache (El Amrani et al., 2002a; Leone et al., 2001), and recently in paroxysmal

hemicrania (Cohen et al., 2006). These syndromes are so rare that an accurate evaluation of their genetic inheritance is difficult, although a primarily inherited basis seems a reasonable way to think about the underlying determinant for these syndromes.

6.11 Triggers

It is known that the following can trigger SUNCT attacks: touching the face or scalp, washing, shaving, chewing, eating, brushing teeth, talking and coughing (Pareja and Sjaastad, 1997). Additional to this list the following potential triggers are included: washing or brushing the hair, light (including sunlight and fluorescent lights), blowing the nose, exercise, and showering. Movement of the neck has previously been shown either to precipitate or abort an attack (Calvo et al., 2004; Pareja and Sjaastad, 1997; Sjaastad et al., 1989). Triggers which are characteristically associated with CH, such as alcohol, smoke, strong smells and a warm environment (Matharu and Goadsby, 2002b), can trigger SUNCT or SUNA in a small proportion of patients. It is known that patients can have a mixture of spontaneous and triggered attacks, but purely triggered attacks (2 % in this series) are hitherto unreported. This may be due to the fact that purely triggered attacks have been previously diagnosed as trigeminal neuralgia. It is therefore useful to recognise that some patients with SUNCT syndrome may experience only triggered, and not spontaneous, attacks.

6.12 Refractory period

Unlike trigeminal neuralgia (TN), SUNCT patients have generally been thought not to have a refractory period (Matharu et al., 2003a; Pareja et al., 1997). This case series bears out the general lack of a refractory period between attacks, so that 92 % of all patients can experience one attack spontaneously occurring immediately after the previous one, or that they can trigger an attack immediately on top of the previous one. This serves as a good clinical feature to distinguish TN and SUNCT, and should be asked of all patients who are suspected to have SUNCT or TN.

6.13 Neurological examination

Generally the neurological examination is normal in SUNCT. There are some reports of allodynia or hyperaesthesia in the face (Graff-Radford, 2000; Pareja et al., 1997; Raimondi and Gardella, 1998; Sabatowski et al., 2001), and a case of post-traumatic SUNCT with a sensory deficit in the first distribution of the trigeminal nerve (Putzki et al., 2005), and one with a persistent ipsilateral Horner's syndrome (Prakash and Lo, 2004). This series includes six patients with SUNCT (12 %) with abnormal sensation to pinprick in V₁ and V₂, and one with SUNA (11 %). Interestingly only one patient had hyperaesthesia (#46). He also had vascular loops compressing on his trigeminal nerve root bilaterally. The hyperaesthesia was only on the side ipsilateral to the pain. Five of six SUNCT patients had reduced sensation to pinprick, and in none of them was the SUNCT attributable to a structural cause. Therefore reduced facial sensation may occur in SUNCT and SUNA as a normal part of the syndromes. Trigeminal sensory pathways can be impaired in cluster headache as reflected by measurements of trigeminal somatosensory evoked potentials (van Vliet et al., 2003c), and this was thought to be due to higher cortical functions or central neuroplasticity (van Vliet et al., 2003c). This may also be due to hypothalamic activity in SUNCT or SUNA. The hypothalamus is known to have a role in general nociceptive control (Millan et al., 1983), there are direct hypothalamic-trigeminal connections (Malick and Burstein, 1998; Malick et al., 2000), and the hypothalamus is known to have a modulatory role on the nociceptive and autonomic pathways, specifically trigeminovascular nociceptive pathways (Bartsch et al., 2004).

One patient with SUNCT had abnormal facial sensation after an infraorbital nerve block, which did nothing to stop his attacks. This is consistent with the notion that SUNCT is a centrally-driven pain syndrome, as even with iatrogenic reduction of sensation the attacks still occurred. This is also seen in cluster headache, where attacks have continued despite surgical ablation of the trigeminal nerve (Matharu and Goadsby, 2002a).

6.14 Symptomatic SUNCT

Most cases of SUNCT are idiopathic, but there are a few cases in the literature which are secondary to intracranial lesions. These are either due to pituitary lesions or posterior fossa lesions. This study found three cases of pituitary lesions causing SUNCT: two macroadenomas, one of whose symptoms resolved completely and one almost completely on treatment of the pituitary lesion, and one microprolactinoma whose symptoms resolved initially for 8 months, then recurred with return of the tumour. One of the patients with macroadenoma has been reported previously (Matharu et al., 2003c). A patient with a pituitary macroadenoma had experienced symptoms of SUNCT which were labeled as trigeminal neuralgia (Ferrari et al., 1988). SUNCT has been described in patients both with microprolactinomas (Levy et al., 2003) and macroprolactinomas (Massiou et al., 2002; Matharu et al., 2003c), with attacks occurring on the side ipsilateral to the side of the tumour, suggesting a role for a direct or mechanical mode of action in macroadenomas, but this would not account satisfactorily for microadenomas. It has therefore been suggested that the attacks were predominantly neurohormonally mediated rather than by the size or invasiveness of the tumour (Matharu et al., 2003c). It is also interesting to note that headache symptoms can precede pituitary symptoms by 3-10 years (Ferrari et al., 1988; Massiou et al., 2002). It is now seen that headache symptoms can continue beyond the treatment of the tumors as in one of our patients (#20).

Cases of symptomatic SUNCT secondary to a posterior fossa abnormality include the following: ipsilateral cerebellopontine arteriovenous malformations in two patients (Bussone et al., 1991; Morales et al., 1994), a brainstem cavernous haemangioma (De Benedittis, 1996), a posterior fossa lesion associated with HIV/AIDS (Goadsby and Lipton, 1997), severe basilar impression causing pontomedullary compression in a patient with osteogenesis imperfecta (ter Berg and Goadsby, 2001), craniostosis resulting in a foreshortened posterior fossa (Moris et al., 2001) ischaemic brainstem infarction (Penart et al., 2001), and Devic's syndrome (neuromyelitis optica) with lesions in both optic nerves and the medulla oblongata (Kursun et al., 2006). This series reports one new case of SUNCT secondary to an acute event of dizziness and ataxia, with an unusual

configuration in the brainstem and lacune in the thalamus (#2). Moreover there is one case of SUNCT with pathological white matter changes and a lesion in the ipsilateral cerebral peduncle (#52), and also a case of SUNA apparently related to multiple sclerosis with lesions in the midbrain and pons that might account for the pain (#SUNA4).

Rare cases of SUNCT have been reported in association with vascular compression of the trigeminal nerve (Gardella et al., 2001; Koseoglu et al., 2005), in contrast to trigeminal neuralgia, for which the incidence of trigeminal nerve compression is 47-90 % (Kuroiwa et al., 1996; Love and Coakham, 2001; Majoie et al., 1997). In this series only three SUNCT patients (7 %) have vascular compression; one with the compression ipsilateral to the pain (#13), one with bilateral vascular compressions but only unilateral pain (#56), and one with unilateral compression but bilateral pain (#55). The question therefore arises as to the role of trigeminal nerve root compression by vascular loops, as it is possible to have vascular compression without attacks, and also attacks on the side contralateral to the compression. It may be that the vascular loops are incidental findings.

The database includes one SUNCT patient with generalised cerebral white matter lesions (#7), and 2 patients with parietal or parieto-occipital lesions that anatomically may not account for the pain: #57 and #51, who also had an ipsilateral VI nerve and contralateral XII nerve palsy due to a head injury. It is unclear as to whether these lesions were a direct cause of the SUNCT attacks, or whether they are incidental findings unassociated with the headache symptoms. Indeed in both patients with space-occupying lesions, the symptoms persisted even after their excision.

The concept of post-traumatic headache requires that the headache syndrome starts within seven days of sustaining the trauma (Headache Classification Committee of The International Headache Society, 2004). In this series there are two patients (#42 and #52) with onset of SUNCT within one week of trauma. For other SUNCT patients (Table 5.3) the trauma is less acute, although occurring within weeks in each case. However it may remain that these headache syndromes were precipitated as a result of the trauma sustained. Chronic headache following trauma to the head or neck is well described, with

the duration of headache being independent of the type or severity of trauma (Warner, 2000). Axonal injury and shearing effects are well documented in both animals and humans after direct mild to moderate head injury, and physiological changes have been noted after concussion injuries (Saper, 2000). It is therefore plausible to speculate that, just as the dorsal raphe nucleus may sustain a physiological abnormality post-traumatically, and lead to chronic migraine (Raskin et al., 1987), there may be a physiological shift in the hypothalamus following trauma which may lead to the development of SUNCT or SUNA.

6.15 SUNA

SUNA- Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic features, may include SUNCT and simplifies the classification of patients without the C or the T component. However, for the moment given how distinctive SUNCT is clinically, keeping the separation may be useful. SUNA patients have attacks similar to SUNCT in location, duration, frequency and severity, but there is a lack of conjunctival injection, and instead there are other cranial autonomic symptoms (Headache Classification Committee of The International Headache Society, 2004). Pure SUNA is rather rare, having only one other case reported in the literature (Volcy et al., 2005). The clinical phenotype and response to medications are in most other respects very similar to SUNCT. The reason for labelling these patients with the diagnosis of SUNA is partly because SUNCT by definition requires conjunctival injection and tearing, and partly because there may be many more patients in general neurological and clinical practice who have SUNA but have been misdiagnosed due to the lack of autonomic symptoms in the eye. This study reports the only series of patients in the literature with SUNA. Most patients had primary chronic SUNA, with one patient experiencing spontaneous remission, as opposed to the 65 % of SUNCT patients who had episodic SUNCT at some point during their disease.

The site of attacks was more varied for SUNA than SUNCT; particularly the temple, side of the head, and V₃ were affected more in SUNA than in SUNCT. There were no SUNA

patients whose attacks could be triggered by touch, as opposed to 63 % of SUNCT patients in whom touching the face could trigger attacks. Cranial autonomic symptoms were more varied in SUNA, without the duo of conjunctival injection and lacrimation, and with more diverse autonomic symptoms, such as mydriasis and ear flushing, which were not present in SUNCT. Indeed one would predict from the experimental and human physiology that a different involvement of the trigeminal sub-divisions would produce differences in the activation of the cranial autonomic pathways (Goadsby and Lipton, 1997; May et al., 2001). All of these differences, which would be contrary to the usual picture of SUNCT, could account for the under diagnosis of SUNA in the general and neurological clinics. However the basic phenotype of the disease remains the same in SUNCT and SUNA; that is the length, frequency and severity of attacks; the type and temporal character of the pain; the presence of cranial autonomic symptoms, the ability to trigger attacks, the lack of refractory period between attacks, and the nocturnal occurrence, but not preponderance, of attacks. A change to the current classification is therefore proposed for these headache syndromes, based on this series (Table 6.1).

Table 6.1

Proposed diagnostic criteria for SUNCT and SUNA

Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT) or cranial Autonomic features (SUNA)

3.3R Diagnostic criteria:

- A. At least 20 attacks fulfilling criteria B-E
- B. Attacks of short-lasting (1-600 s) unilateral head pain
 - a. orbital, supraorbital, temporal or other trigeminal distribution of moderate or severe pain
 - b. occurring as
 - i. Single stabs
 - ii. Groups of stabs
 - iii. In a saw-tooth pattern
 - c. Triggerable without a refractory period
- C. Pain is accompanied ipsilaterally by either:
 - a. Conjunctival injection and Tearing (SUNCT), or,
 - b. One or more of the following cranial Autonomic symptoms (SUNA)
 - i. conjunctival injection, or tearing, but not both
 - ii. nasal congestion and/or rhinorrhoea
 - iii. eyelid oedema
 - iv. ipsilateral sense of aural fullness or peri-aural swelling
 - v. ipsilateral forehead and facial sweating
 - vi. ipsilateral miosis and/or ptosis
- D. Attacks occur with a frequency of ≥ 1 per day for more than half the time when the disorder is active
- E. Not attributed to another disorder

A 3.3.1 Episodic SUNCT/SUNA

Description: SUNA attacks occurring for 7 days to 1 year with pain free intervals longer than 1 month

A 3.3.2 Chronic SUNCT/SUNA

Description: At least 2 attack periods last 7 days to 1 year separated by remission periods of less than one month (untreated).

6.17 Summary

A prospective clinical study in 52 patients with SUNCT and SUNA was performed. This study revealed 43 patients with SUNCT and nine with SUNA. The clinical phenotype of both conditions has been characterised. Suggestions of changes to the International Headache Society classification have been made, based on these cases. In view of the widely varying range of attack character, frequency and duration, it appears that many patients were misdiagnosed with conditions such as trigeminal neuralgia and other trigeminal autonomic cephalgias (TACs), such as cluster headache and paroxysmal hemicrania. A system is proposed in order to assess the temporal pattern, duration and frequency of attacks in terms of stabs, groups of stabs and saw-tooth attacks; and the concept of attack load in terms of minutes of pain per day. The concept of a constant background pain in these syndromes is noted, along with the implication this has on patients with a history of migraine, migraine biology and analgesic overuse. The ability to trigger attacks is observed, specifically the concept of attacks which are 100% triggered; and the overwhelming lack of a refractory period between attacks that is now characteristic of SUNCT/SUNA. In terms of symptomatic SUNCT/SUNA, the importance of posterior fossa abnormalities is explored. The concept of post-traumatic SUNCT and SUNA has been discussed; as has the issue of vascular loops compressing on the trigeminal nerve root, for which the evidence as a causative factor to the pain is much less robust than in trigeminal neuralgia.

Chapter 7

Results: Clinical Study of Treatment of SUNCT and SUNA

7.1 Diagnosis and time to diagnosis

All patients gave information about practitioners consulted prior to consulting or being referred to the National Hospital for Neurology and Neurosurgery. All patients had seen at least one GP. Thirty-eight SUNCT patients (88%) and 8 SUNA patients (89%) had seen another neurologist prior to consultation at the National Hospital. In total, 3 patients had seen dentists, 4 had seen ENT surgeons, 4 had seen ophthalmologists and 3 had seen pain specialists.

The diagnosis of SUNCT was made by the neurologists at the National Hospital for Neurology and Neurosurgery in 30 patients (70%). Diagnoses were made by neurologists at other hospitals in 12 (28%) of SUNCT patients. The diagnosis of SUNA was made entirely by neurologists at the National Hospital for Neurology and Neurosurgery. It took an average of 6.7 years from the onset of SUNCT (median 5, range 0.25-24 years) for a diagnosis to be made, and a mean 7.1 years (median 2, range 1-46 years) for the diagnosis of SUNA. These are illustrated in Table 7.1.

7.2 Previous Diagnoses

Patients were diagnosed with a number of conditions before their SUNCT or SUNA was diagnosed. These conditions include: trigeminal neuralgia (18 SUNCT, 1 SUNA), cluster headache (11 SUNCT, 1 SUNA), paroxysmal hemicrania (4 SUNCT, 4 SUNA), trigeminal autonomic cephalgia not otherwise specified (6 SUNCT, 1 SUNA), hemicrania continua (1 SUNCT, 1 SUNA), migraine (5 SUNCT, 2 SUNA), dental problems (2 SUNCT), post herpetic neuralgia (2 SUNCT), demyelination (2 SUNCT); and others including post herpetic neuralgia, cerebral vasculitis, migrainous facial neuralgia, psychosomatic symptoms, chronic daily headache with analgesic overuse, Bell's palsy, multiple sclerosis, seizures, primary stabbing headache, stress and temporal

arteritis in 1 SUNCT patient each; and temporal arteritis in 1 SUNA patient. 3 SUNA patients (33%) had been previously diagnosed with SUNCT. These are illustrated in Table 7.2.

Table 7.1

Practitioners seen prior to diagnosis of SUNCT/SUNA, final diagnostician, and years to diagnosis

Practitioners seen prior to diagnosis	SUNCT	SUNA	total
GP	43 (100%)	9 (100%)	52 (100%)
Neurologist	38 (88%)	8 (89%)	46 (88%)
Dentist	3 (7%)	0 (0%)	3 (6%)
ENT surgeon	3 (7%)	1 (11%)	4 (8%)
Ophthalmologist	3 (1%)	1 (11%)	4 (8%)
Pain Specialist	2 (5%)	1 (11%)	3 (6%)
Diagnosis made by:	SUNCT	SUNA	total
Other neurologist	12 (28%)	0 (0%)	12 (23%)
Neurologist at NHNN	30 (70%)	9 (100%)	39 (75%)
unknown	1 (2%)	0 (0%)	1 (2%)
Years to diagnosis			
mean	6.7	7.1	
median	5	2	
range of years to diagnosis	0.25-24	1-46 years	

Table 7.2

Diagnoses made prior to SUNCT/SUNA

	SUNCT	SUNA
Trigeminal neuralgia	18 (42%)	1 (11%)
Cluster headache	11 (26%)	1 (11%)
Paroxysmal hemicrania	4 (9%)	4 (44%)
TAC not otherwise specified	6 (14%)	1 (11%)
Hemicrania continua	1 (2%)	1 (11%)
Migraine	5 (12%)	2 (22%)
Other	13 (30%)	1 (11%)
SUNCT	n/a	3 (33%) *

* missing C or T (conjunctival injection or lacrimation)

Treatments

7.3 Abortive Therapies

Triptans

Eleven SUNCT patients and 4 SUNA patients had triptans. Five SUNCT patients had oral triptans (sumatriptan, rizatriptan, naratriptan) with no effect. Subcutaneous sumatriptan 6mg in SUNCT aborted the attacks in one patient, reduced the length of the attacks in 1 patient and had no effect in a further 3 patients. It had no effect in all 3 SUNA patients who tried it. Intranasal sumatriptan 20mg had a minimal effect in one SUNCT patient and no effect in 1 SUNA patient.

Oxygen

Oxygen at high flow (100%, 9-12 l/min) was delivered to 10 patients with SUNCT and 5 with SUNA. It had no effect in 7 of the SUNCT patients, and no effect in any of the SUNA patients. In one SUNCT patient it changed the quality of the attacks from sharp to burning, one had a minimal effect on the attacks, and one patient reported that oxygen was useful in his concomitant cluster headache (#34). Oxygen at low flow (4 l/min) had no effect in 1 SUNCT patient.

Intranasal Lidocaine

Intranasal lidocaine had a moderate effect in one SUNCT patient and one SUNA patient, and minimal to no effect in 5 SUNCT and 2 SUNA patients. These are illustrated in Table 7.3.

Table 7.3
Abortive therapies

	SUNCT			SUNA		
	Number of patients	effective	ineffective	Number of patients	effective	ineffective
sumatriptan subcutaneous	5	2 (40%)	3 (60%)	3	0 (0%)	3 (100%)
sumatriptan intranasal	1	0 (0%)	1 (100%)	1	0 (0%)	1 (100%)
oral triptans	5	0 (0%)	5 (100%)	0	0	0
oxygen high flow	10	0 (0%)	10 (100%)	5	0 (0%)	5 (100%)
oxygen low flow	1	0 (0%)	1 (100%)	0	0	0
intranasal lidocaine or xylocaine	6	1 (17%)	5 (83%)	3	1 (33%)	2 (67%)

Table 7.4
Short-term preventive agents; intramuscular indomethacin and intravenous lidocaine

	SUNCT			SUNA		
	Number of patients	effective	ineffective	Number of patients	effective	ineffective
Indomethacin test	12	0 (0%)	12 (100%)	4	0 (0%)	4 (100%)
oral indomethacin	19	2 (11%)	17 (89%)	4	0 (0%)	4 (100%)
intravenous lidocaine	11	11 (100%)	0 (0%)	4	4 (100%)	0 (0%)

Table 7.5
Indotest in SUNCT and SUNA

patient number	diagnosis	number of attacks/24 hours		effect on background pain
		post placebo	post indomethacin	
2	SUNCT	4	4	
12	SUNCT	same	same	
13	SUNCT	5-15 attacks of a few seconds, 5 attacks lasting minutes	some reduction in the longer attacks	
27	SUNCT	same	same	
29	SUNCT	8 attacks without indomethacin	9	
34	SUNCT	same	same	
36	SUNCT	5/day	5/day	
53	SUNCT	same	same	
56	SUNCT	7	5	
57	SUNCT	6	7	
39	SUNCT	indotest at another hospital	reported as negative	
55	SUNCT	indotest at another hospital	reported as negative	
SUNA1	SUNA	22	9	reduced for 4-5 hours, not after placebo
SUNA44	SUNA	11	16	
SUNA41	SUNA	16	22	
SUNA59	SUNA	7	6	no significant changes for either

7.4 Short-term Preventive Medications

Indomethacin

A modified *Indotest* was performed in 12 SUNCT and 4 SUNA patients, with single-blinded placebo-controlled indomethacin injections, and their responses were recorded in terms of number of attacks in the 24 hours after each treatment. In one SUNCT patient (#29) the response to placebo was lost in the notes. Two SUNCT patients had this procedure done at other hospitals, and their results were reported in the notes. The modified *Indotest* was reported as negative in 100% of these patients; that is it did not significantly reduce the number, frequency or duration of their attacks as compared to a saline injection given in a blinded fashion. Although in 1 patient (#SUNA1), there was a reduction in the number of attacks and some reduction in the background pain, this was not considered to be a clearly positive result for indomethacin. This is illustrated in Tables 7.4 and 7.5.

Oral indomethacin was given in doses of 50mg-300mg a day in 19 SUNCT and 4 SUNA patients. It was ineffective in 17 SUNCT (89%) and all 4 SUNA patients (100%). It had a good effect for a few months at 100mg daily in one SUNCT patient, before the effect wore off. It reduced the intensity of the attacks at 300mg daily in one SUNCT patient. It caused side effects in 2 SUNCT and 2 SUNA patients, including abdominal pain, haematuria and rectal bleeding.

Intravenous lidocaine

Intravenous lidocaine at doses of up to 3.5 mg/kg/minute was infused into 11 SUNCT and 4 SUNA patients. One SUNCT patient had the infusion on two occasions. It had a moderate to good effect in all 11 patients. It rendered 7 SUNCT patients pain free for times varying between the duration of the infusion to 6 months. In 2 SUNCT patients it reduced the severity of their attacks, and in a further patient it reduced the severity of the background pain and the frequency of the attacks. In one patient (#13) the attacks were completely abolished, and the patient was started on topiramate up to a dose of 150mg daily towards the end of the infusion, so it is unclear as to how long the infusion would

have rendered him pain free. Patients suffered side effects of cognitive symptoms (7 patients), including depression (2 patients), hallucinations, paranoid ideations and agitation. One patient (#34) suffered palpitations and had atrial fibrillation at 2.45mg/kg/hour, which resolved on reducing the flow rate. One patient had a tachycardia and one had bradycardia with heart rate 45-49 bpm, both of which resolved on reducing the rate. In the four SUNA patients, all were rendered pain free or almost pain free for 2 days to 12 weeks. Two of these patients suffered with emotional lability for the duration of the infusion.

Most patients were not taking concomitant preventive medications during the infusions. There are 2 exceptions: #13 who was started on topiramate up to a dose of 150mg daily towards the end of the infusion, and #21 who was taking gabapentin 3600mg daily throughout his hospital admission. These are illustrated in Table 7.4, and in more detail in Table 7.6. Figure 7.1 is a graphical representation of patient #SUNA41, who had the most striking result in that a 6-day lidocaine infusion at a maximum of 3mg/minute (2.5mg/kg/hour) rendered her pain free for 12 weeks.

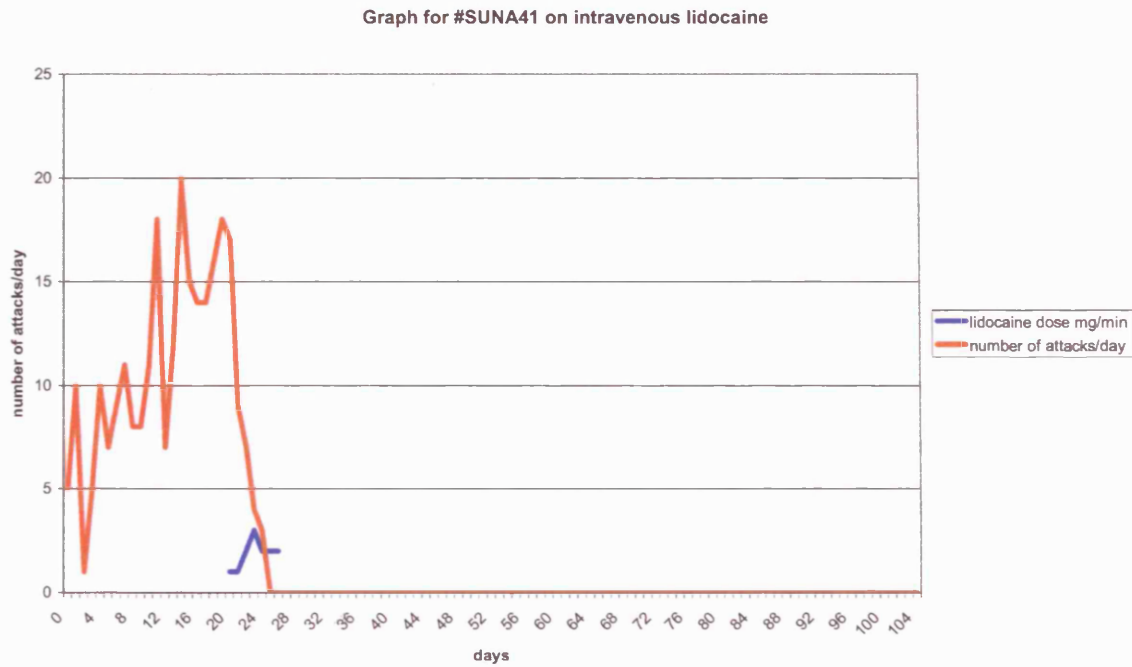
One SUNCT patient (#36), in whom the subcutaneous sumatriptan had a moderate effect in reducing the length of the attacks, received an infusion of intravenous dihydroergotamine 3mg/24 hours for 3 days, and it had a moderate effect in reducing the length and frequency of her attacks. This was the same patient for whom subcutaneous sumatriptan reduced the attack length.

Table 7.6
Intravenous Lidocaine in SUNCT and SUNA

Patient no	diagnosis	weight/ kg	maximum dose lidocaine		duration of infusion	daily number of attacks		other effect	duration of effect	side effects
			mg/min	mg/kg/hour		pre lidocaine	on lidocaine			
2	SUNCT	102.5	4	2.34	7	5	0	eliminated background pain	1.5 weeks	
7	SUNCT	87.5	3	2.06	5	19	0		3 weeks	nausea, depression
12	SUNCT	72	3	2.5	2	many	few		1 day	hallucinations, anxiety
13	SUNCT	unknown	2		4	8	0	highly effective in 1 hour	unsure	bradycardia
21	SUNCT	132	3	1.37	7	24	5	eliminated background pain	1 month	mildly irritable
22	Episodic SUNCT	90.5	2	1.33	3	5	0		6 months	tachycardia, facial flushing
53	SUNCT	62	3.7	3.5	5	same	same	reduced severity of attacks	duration infusion	agitated, tearful
27	SUNCT	unknown	2		3	85	0		duration infusion	
34	SUNCT	98	4	2.45	5	<150	0	reduced background pain	duration infusion	atrial fibrillation
36	SUNCT	57	3.5 (1st admission)	3.4	4	3.5	0	reduced background pain	2 days	paranoid
36	SUNCT	57	3 (2nd admission)	3.16	4	6	0	reduced background pain	2.5 days	paranoid
57	SUNCT	107	4	2.24	4	16	3	reduced length & frequency	duration infusion	depressed
SUNA1	SUNA	70	3	2.57	6	14	1		2 days	agitated, nightmares
SUNA44	SUNA	88	3	2.05	5	10	0	autonomic symptoms without pain	2 days	tearful
SUNA41	SUNA	71	3	2.54	6	18	0	eliminated background pain	12 weeks	dizzy
SUNA59	SUNA	83	2	1.45	6	9	3	eliminated background pain	1 week	

Figure 7.1

Graph showing number of attacks per day for Patient SUNA41 before and after intravenous lidocaine



7.5 Preventive medications

7.5.1 Lamotrigine

Twenty-five SUNCT and four SUNA patients received lamotrigine in doses of 50–400mg daily in an open-label fashion. In nine SUNCT patients and one SUNA patient the lamotrigine had a good effect in suppressing their attacks. Lamotrigine was moderately effective in 8 SUNCT patients, either alone or in combination with gabapentin, amitriptyline, topiramate, or carbamazepine. In 6 of these patients the lamotrigine had to be stopped before the optimum dose was achieved, because they were experiencing side effects. In 8 SUNCT and 3 SUNA patients there was no beneficial effect; indeed lamotrigine actually made two patients' SUNCT attacks worse.

Side effects were reported in 11 patients; these included anaphylactic reaction in 2 patients, skin rash in 4 patients, and also arthralgia, cognitive slowing, flu-like symptoms, mood swings, and sedation. In one patient the lamotrigine suppressed the SUNCT but made her migraine worse.

7.5.2 Topiramate

Twenty-one patients with SUNCT received topiramate in an open-label fashion at doses of 25–400mg daily. There was a moderate to good effect in 11 patients (52%), nine of whom reported a good effect in abolishing their attacks. One patient combined topiramate with lamotrigine. In 10 SUNCT (48%) patients there was little or no beneficial effect of topiramate. In one SUNCT patient the attacks were worsened on topiramate. Side effects were reported in 9 SUNCT patients (43%); these included renal stones in 2 patients, which necessitated withdrawal of topiramate, peripheral paraesthesiae (2 patients), anorexia and weight loss (2 patients), and cognitive side effects including sedation, mood swings and memory loss (7 patients).

One patient with SUNA received topiramate 800mg daily. There was no beneficial effect at this dose, although it improved her migraine headaches.

7.5.3 Carbamazepine

Thirty-six patients with SUNCT and 5 with SUNA received carbamazepine at doses of 100-1600mg daily. There was a good effect in 4 SUNCT patients, either alone or in combination with lamotrigine, although in 2 of these this could have coincided with the end of their bout of attacks. In 10 SUNCT and 1 SUNA patient there was a moderate effect in that their attacks were reduced but not suppressed completely. In 22 SUNCT and 4 SUNA patients there was little or no beneficial effect of carbamazepine. Side effects were reported in 2 SUNA and 14 SUNCT patients; these included drowsiness, skin rash and cognitive slowing.

7.5.4 Gabapentin

Twenty-two patients with SUNCT and 5 patients with SUNA received gabapentin at doses of 600-3600mg daily. In 1 SUNCT patient there was complete abolition of attacks. In 9 SUNCT patients and 3 SUNA patients gabapentin was moderately effective, either alone or in combination with other drugs such as amitriptyline, lamotrigine or carbamazepine. There was minimal to no effect in 12 SUNCT and 2 SUNA patients. In 2 SUNCT patients their attacks were actually worsened on the gabapentin. Side effects were reported in 7 SUNCT (32%) and 2 SUNA patients (40%). These included skin rash, sedation, mood swings, weight gain, diarrhoea and arthralgia.

7.5.5 Valproate

Sodium Valproate was given to 9 SUNCT patients and one SUNA patient, at doses of 400- 1600mg daily. In all patients there was no effect.

7.5.6 Amitriptyline

Twenty-four SUNCT patients and 7 SUNA patients received amitriptyline at doses of 25-150mg daily. In 23 SUNCT and all 7 SUNA patients there was no effect. In one SUNCT patient there was a moderate effect at 150mg daily, but there were side effects of dry mouth and drowsiness.

7.5.7 Melatonin

One SUNCT patient and two SUNA patients received melatonin at 9mg daily. In the SUNCT patient there was a reduction in the frequency of his attacks. In one SUNA patient there was a mild effect with melatonin but it made her migraine worse. It was ineffective in the other SUNA patient and caused drowsiness as an adverse effect.

7.5.8 Pregabalin

Two SUNCT patients and one SUNA patient received pregabalin at doses of 150-600mg. This had a good effect in one SUNCT patient which wore off after a few months, a moderate effect in 1 SUNCT patient in combination with topiramate and a greater occipital nerve injection, and minimal to no effect in the SUNA patient. Two patients experienced cognitive side effects which necessitated withdrawal of the pregabalin.

7.5.9 Steroids

Twelve SUNCT patients and 2 SUNA patients received prednisolone at doses of 30-80mg daily. In 2 patients this had a moderate effect (#20 who received 30mg daily in combination with cabergoline and octreotide after hypophysectomy for a pituitary macroadenoma, and #9 who took 80mg of prednisolone daily). In the remaining 10 SUNCT and 2 SUNA patients there was no effect.

7.5.10 Verapamil

Nine patients with SUNCT received verapamil at doses between 120 and 800mg daily. It had a mild effect in one patient at 800mg but made him drowsy, and had no effect in the other patients. In SUNA, verapamil at 240 mg/day had a good effect in one patient (MC40) with a good effect in reducing his other TAC (cluster headache) as well.

7.5.11 Lithium

Two patients with SUNCT and one with SUNA had lithium, at therapeutic doses with serum lithium levels 0.8-1-1umol/l. In all 3 patients there was no effect. These are illustrated in Table 7.7.

Table 7.7

Preventive medications and greater occipital nerve block (GON) in SUNCT/ SUNA

	SUNCT			SUNA		
	No. of patients	effective	ineffective	No. of patients	effective	ineffective
lamotrigine (LTG)	25	17 (68%)	8 (32%)	4	1 (25%)	3 (75%)
topiramate (TPM)	21	11 (52%)	10 (48%)	1	0 (0%)	1 (100%)
carbamazepine (CBZ)	36	14 (39%)	22 (61%)	5	1 (20%)	4 (80%)
gabapentin (GBP)	22	10 (45%)	12 (55%)	5	3 (60%)	2 (40%)
valproate (VPA)	9	0 (0%)	9 (100%)	1	0 (0%)	1 (100%)
amitriptyline (Ami)	24	1 (4%)	23 (96%)	7	0 (0%)	7 (100%)
melatonin	1	1 (100%)	0 (0%)	2	0 (0%)	1 (100%)
pregabalin (PRG)	2	2 (100%)	0 (0%)	1	0 (0%)	1 (100%)
prednisolone	12	2 (17%)	10 (83%)	2	0 (0%)	2 (100%)
verapamil	9	0 (0%)	9 (100%)	1	1 (100%)	0 (0%)
lithium	2	0 (0%)	2 (100%)	1	0 (0%)	1 (100%)
combinations						
GBP + CBZ	1	0 (0%)	1 (100%)	1	1 (100%)	0 (0%)
GBP + CBZ + Ami	1	1 (100%)	0 (0%)			
TPM + CBZ	1	1 (100%)	0 (0%)			
TPM + CBZ + Ami	1	0 (0%)	1 (100%)			
GBP + LTG	2	1 (50%)	1 (50%)			
GBP + LTG + Ami	1	1 (100%)	0 (0%)			
TPM + LTG	2	2 (100%)	0 (0%)			
LTG + CBZ	1	1 (100%)	0 (0%)			
GBP + Ami + NSAID	2	1 (50%)	1 (50%)			
CBZ + Ami	1	1 (100%)	0 (0%)			
TPM + PRG + GON	1	1 (100%)	0 (0%)			
GON injection	8	5 (63%)	3 (37%)	1	0 (0%)	1 (100%)

7.5.12 Other Preventive Medications

One SUNCT patient had methysergide 4mg daily. Four SUNCT patients and 2 SUNA patients had propranolol up to 160 mg daily. None of these had any effect. Also tried were: paracetamol/codeine preparations (18 patients), ibuprofen (10 patients), diclofenac (6 patients), aspirin (5 patients), codeine (4 patients), dothiepin (4 patients), clonazepam (4 patients), celecoxib (3 patients), morphine (3 patients), pizotifen (3 patients); 2 patients each with oxcarbazepine, diazepam, phenytoin, lofepramine, fluoxetine, baclofen; and 1 patient each with naproxen, rofecoxib, leviteracetam, tizanidine, prothiaden, sertraline, mirtazapine, cannabis, ketamine, chlorpromazine, nabilone, and intranasal EMLA. All of these had no effect apart from a mild effect with ibuprofen, diclofenac and morphine in 1 patient each. Leviteracetam 1000 mg daily in one patient made the SUNCT worse.

7.5.13 Combinations of Preventives

Combinations of preventive medications were used in 11 SUNCT and 1 SUNA patient. Some patients had more than one combination. The following combinations of preventives were used in SUNCT: gabapentin and carbamazepine (ineffective in one patient, effective in one patient with addition of amitriptyline), topiramate and carbamazepine (effective in one patient, and in one further patient with addition of amitriptyline), gabapentin and lamotrigine (effective in one patient, ineffective in one patient, effective in one patient with addition of amitriptyline), topiramate and lamotrigine (effective in 2 patients), lamotrigine and carbamazepine (effective in one patient), gabapentin and amitriptyline and a NSAID (effective in one and ineffective in one patient), carbamazepine and amitriptyline (effective in one patient), and topiramate and pregabalin plus a greater occipital nerve injection (effective in one patient). A combination of gabapentin and carbamazepine was effective in one SUNA patient. These are illustrated in Table 7.7.

7.6 SUNCT secondary to pituitary disease

Three patients had SUNCT secondary to pituitary disease. One (#20) had a macroadenoma for which he underwent a transsphenoidal hypophysectomy and radiotherapy. His SUNCT persisted and he was treated with cabergoline 500mg twice a week, prednisolone 30 mg daily, and octreotide injections once a month, which almost abolished his SUNCT.

The second (#25) had a microadenoma which was resected in 1987 and a residual microadenoma removed in 2002, with some resolution of her SUNCT after the second resection. She was treated with bromocriptine, cabergoline and octreotide, all of which increased her SUNCT symptoms. She had a good effect with Lamotrigine 125mg daily, but this gave her side effects of a skin rash and flu-like symptoms.

The third patient (#37) had SUNCT secondary to a large prolactinoma. His SUNCT resolved on both bromocriptine 2.5mg twice daily, and cabergoline 1.5mg/week, with corresponding resolution of his pituitary symptoms and prolactin levels. His case has been previously reported (Matharu et al., 2003c).

7.7 Non-pharmacological manipulations

7.7.1 Greater Occipital Nerve Injection

Eight SUNCT patients and one SUNA patient underwent injection of 2% lidocaine and 80mg depomedrone in the region of the ipsilateral greater occipital nerve (GON), the method of which has been described previously (Shields et al., 2004).

Five SUNCT patients (63%) experienced a good effect in that it rendered them pain free for one week to 6 months. In one of these patients the attacks returned after 2 weeks but on the contralateral side to the injection. In 3 SUNCT patients (37%) there was no effect, and the SUNA patient had a minimal transient effect. These are illustrated in Table 7.7.

7.7.2 Other non-pharmacological manipulations

Six SUNCT patients underwent other procedures. Some patients had more than one intervention. These were: microvascular decompression, sphenopalatine marcaine injection, retrogasserian alcohol block, all of which had no effect at all. One patient had a supraorbital nerve injection and one had an infraorbital nerve injection which caused numbness but the attacks were still triggerable. One patient had a C2 nerve block which rendered her pain free for one year. One had a trigeminal nerve procedure otherwise unspecified, which rendered her pain free for 3 years.

Two SUNCT patients and one SUNA patient had TENS therapy (Transcutaneous Electrical Nerve Stimulation); in all three patients this was ineffective.

7.8 Alternative therapies

Eleven SUNCT and one SUNA patients sought alternative therapies. Eight SUNCT and one SUNA patient had acupuncture. This had a good effect in one patient, rendering him painfree for weeks at a time, with reproducible effects on repeated treatments. It had a moderate effect in 2 patients and a mild effect in one patient. It had no effect in 4 SUNCT patients and the SUNA patient. Indian head massage had no effect in 3 SUNCT patients. Osteopathy had a mild effect in one patient, and homeopathy was ineffective in one patient. These are illustrated in Table 7.8.

Table 7.8

Acupuncture and other alternative therapies in SUNCT and SUNA

	SUNCT			SUNA		
	Number of patients	effective	ineffective	Number of patients	effective	ineffective
acupuncture	8	5 (63%)	3 (37%)	1	0 (0%)	1 (100%)
Indian head massage	3	0 (0%)	3 (100%)			
osteopathy	1	0 (0%)	1 (100%)			
homeopathy	1	0 (0%)	1 (100%)			

7.9 Triggering

There was no nitroglycerin-triggering of attacks in 5 of 6 SUNCT patients (83%), and both SUNA patients. The one patient in whom GTN triggered an attack (#20) had SUNCT secondary to a prolactinoma. GTN did not trigger migraine in the 2 SUNCT and 2 SUNA patients who had a history of migraine, although it did cause a generalised featureless headache in one SUNCT patient (#35). This is illustrated in Table 7.9.

In five of 6 SUNCT patients (83%) and both SUNA patients (100%), sublingual GTN would not trigger an attack. Two SUNCT and both SUNA patients had personal histories of migraine. In one patient with no previous history of migraine, nor any family history of migraine (#35), the GTN triggered a generalised throbbing headache with nausea which lasted for one hour, but not an attack of SUNCT. One SUNCT patient (#20) had one attack triggered by GTN. This patient had SUNCT secondary to a pituitary macroadenoma. These results are tabulated in Table 7.9.

Table 7.9

Concomitant migraine, nitroglycerin triggering and oxygen

Patient number	Diagnosis	Effect of GTN	Effect of oxygen	Migraine
7	SUNCT	-	no effect	no
12	SUNCT	negative	no effect	no
13	SUNCT		mild	no
20	secondary SUNCT	positive	-	no
22	SUNCT	-	no effect	yes
29	SUNCT	negative	no effect	yes
34	SUNCT	-	no effect	yes and CH
35	SUNCT	no SUNCT but generalised headache	-	no
36	SUNCT	negative	no effect	no
46	SUNCT	negative	no effect at low flow	yes
53	SUNCT	-	no effect	yes
56	SUNCT	-	no effect	no
57	SUNCT	-	changed quality of pain	no
SUNA1	SUNA	-	minimal	no
SUNA40	SUNA	-	no effect	yes and CH
SUNA41	SUNA	negative	no effect	yes
SUNA44	SUNA	-	no effect	yes
SUNA59	SUNA	negative	no effect	yes

Chapter 8

Results: Double-blind, placebo-controlled trial of topiramate in SUNCT and SUNA

All 5 patients completed the trial. One patient (#5) only gave data for attack frequency, and not for the duration of his attacks.

One patient (#47) had a good effect whilst on placebo, with complete cessation of his attacks. On topiramate there was an increase of both attack frequency and attack load. The total headache load was the same as attack load, as he had no other headache syndromes.

One patient (#21) had increased frequency of his attacks on topiramate, although the attack load and headache load in terms of minutes per day of pain, were both reduced on topiramate. The headache load was also reduced on placebo. This patient had no other primary headache syndromes documented; however his 'other headaches' reported in this study were painful episodes lasting 25-720 minutes (mean 174 minutes). These could have been prolonged attacks of SUNCT, as this patient was known to suffer groups of stabs of SUNCT; each individual stab would last one second but the groups could go on for an hour or more. In this case the patient recorded each of these prolonged episodes as one attack. The analysis was done both including and excluding these episodes.

The third patient (#27) had complete cessation of his attacks on topiramate, and a milder but less significant reduction of frequency of his attacks (15% reduction) on placebo. He did not give any information as to the length of each attack.

The fourth patient (#34) had a mildly reduced SUNCT attack load on topiramate, but an increase in headache load on topiramate when his other headache syndromes were taken into account. There was no beneficial effect on placebo.

The fifth patient (#38) had an insignificant reduction of his attack frequency on topiramate, but an increase in attack load, which was the same as his total headache load. He had a history of episodic migraine, but had no actual migraine attacks during the trial. He had no beneficial effect on placebo.

The results are shown in Table 8.1.

Side effects

One patient (#8) reported peripheral paraesthesiae on topiramate. One patient (#4) reported peripheral paraesthesiae on both treatments, and also had dull headache attacks whilst on both treatments, which were not related to his SUNCT or migraine, and not recorded as such. He had one episode of diplopia lasting an hour on placebo, and reported indigestion whilst on topiramate.

Table 8.1

Change in attack frequency for placebo and topiramate

	Patient				
Patient number	#47	#21	#27	#34	#38
Age	72	54	60	59	51
Episodic or chronic	Episodic	Primary chronic	Secondary chronic	Primary chronic	Episodic
Other headaches	Nil	Nil	Nil	migraine with aura cluster headache	Episodic migraine
Mean duration of SUNCT attacks	120-1800sec	1 sec stabs, up to 3600sec groups	5 sec	1 sec stabs, 300sec groups	60 sec
Daily frequency of attacks pre plac/max plac	7; 0	13; 19	140; 118	13; 16	10; 9
% change in frequency on placebo	-100%	+52%	-15%	+22%	-10%
Daily frequency of attacks pre TPM/max TPM	2; 35	23; 28	138; 0	10, 13	6; 5
% change in frequency on TPM	+2063%	+19%	-100%	+27%	-18%
Daily attack load pre plac/max plac	2.93; 0	5.42; 15.1	n/a	92.6; 271.1	10.7; 15.5
% change in attack load on placebo	-100%	+178%	n/a	+192%	+45.2%
Daily attack load pre TPM/max TPM	56.9; 580	33.1; 9.56	n/a	197; 164	3.15; 8.175
% change in attack load on TPM	+920%	-71.1%	n/a	-16.8%	+160%
Total headache load pre plac/max plac	2.93; 0	5945; 160	n/a	105; 271	10.7; 15.5
% change total headache load on placebo	-100%	-97.3%	n/a	+159%	+45.2%
Total headache load pre TPM/max TPM	56.9; 580	161; 9.56	n/a	207; 232	3.15; 8.175
% change total headache load on TPM	+920%	-94%	n/a	+12.2%	+160%
Effect of placebo on frequency	1	0	0	0	0
Effect of placebo on attack load	1	0	n/a	0	0
Effect of placebo on headache load	1	1	n/a	0	0
Effect of TPM on frequency	0	0	1	0	0
Effect of TPM on attack load	0	1	n/a	0	0
Effect of TPM on headache load	0	1	n/a	0	0

Key: plac = placebo, TPM = topiramate, max TPM = maximum dose topiramate

Chapter 9

Results: Double-blind, placebo-controlled trial of lamotrigine in SUNCT and SUNA

Six patients with SUNCT and one with SUNA were screened for the study. Other patients were excluded because they were already taking lamotrigine, or had experienced side effects on it previously. Some patients declined to participate in the study as they were already established on an effective preventive medication, or did not want to take a placebo for a few months with the prospect of the attacks being uncontrolled during that time.

3 SUNCT and 1 SUNA patient were randomised to the study. Of the other 3 patients, 2 had episodic SUNCT and went into remission, and one was well controlled on carbamazepine, so declined entry to the study.

Of the 4 patients randomised, only one SUNCT patient (#33) completed the trial and returned a full dataset of results. One patient withdrew from the study after 2 weeks because the pain of the SUNCT was too great after he had stopped his prior preventive medications, and he was not prepared to take a placebo. One SUNCT and one SUNA patient completed the study but did not complete any diaries. They reported that neither lamotrigine nor placebo had any beneficial effect on their attacks. Both patients had minor side effects of some nausea, myalgia, tiredness and mild cognitive difficulties, which did not necessitate withdrawal of the drug in either patient. In one patient the side effect was on lamotrigine and in the other one the side effect was on placebo.

An 'n of 1' study approach was used for the one complete dataset. It was found that neither lamotrigine nor placebo had any effect in suppressing the SUNCT attacks, both in terms of attack frequency (number of attacks/day) or attack load (number of minutes/day).

On lamotrigine, the frequency of attacks increased by 772% and the attack load increased by 680% as compared to the pre-treatment control phase. On placebo, the frequency of attacks increased by 39% and the attack load increased by 21% from the pre-treatment control phase. These are illustrated in Table 9.1.

Table 9.1

Trial of lamotrigine (LTG) in SUNCT; results from 1 patient

	Pre lamotrigine	Max lamotrigine	% change on LTG	Effect of lamotrigine
Frequency; attacks/day	0.786	6.86	+772%	nil
Attack load; minutes/day	6.68	52.1	+680%	nil
	Pre placebo	Max placebo	% change on placebo	Effect of placebo
Frequency; attacks/day	1.08	1.5	+39.3%	nil
Attack load; minutes/day	0.602	0.728	+20.8%	nil

Chapter 10

Discussion: Treatment in SUNCT and SUNA

10.1 Time to diagnosis, practitioners seen, and previous diagnoses

For SUNCT and SUNA there was a delay to correct diagnosis of 6.7 and 7.1 years respectively. In the extreme case in one SUNA patient, the diagnosis was only made after 46 years of his symptoms. Other diagnoses were considered, including paroxysmal hemicrania, cluster headache and 'TAC not otherwise specified', which shows that SUNCT/SUNA can bear a striking resemblance to the other TACs. Diagnoses such as trigeminal neuralgia, paroxysmal hemicrania, cluster headache and migraine amongst others, have prompted doctors to offer treatments specific to those syndromes. This study now reports the efficacy of these treatments, and in so doing can highlight the differences in response between SUNCT/SUNA and the other primary headache syndromes.

As awareness of SUNCT and SUNA is increased, especially with this current series of 43 SUNCT and 9 SUNA patients, it is hoped that these syndromes will be more readily recognised in clinical neurological practice, and that the treatments offered will reflect those which are reported to be effective in SUNCT and SUNA.

Treatments

10.2 Abortive therapies

Triptans, serotonergic agonists and antagonists

Sumatriptan is used in the abortive therapy of migraine in oral, intranasal, suppository or subcutaneous preparations (Tfelt-Hansen, 1998; Tfelt-Hansen, 2004) and in cluster headache in intranasal or subcutaneous preparations (Sumatriptan Cluster Headache Study Group, 1991; van Vliet et al., 2003a). It has been used either in oral form (100-

300mg daily), or subcutaneously (6mg), with little or no response in SUNCT (Matharu et al., 2003a), as was generally borne out in the current cohort, with 2 exceptions.

Oral or intravenous dihydroergotamine was also ineffective, although it had a moderate effect in one patient (#36), in whom subcutaneous sumatriptan had a moderate effect in reducing the length of her saw-tooth attacks.

Oxygen

High-dose high-flow oxygen has been used to good effect in cluster headache (Fogan, 1985; Kudrow, 1981), but has had little or no effect in SUNCT (Matharu et al., 2003a; Matharu et al., 2004b). It is arguable that any benefit seen in SUNCT patients may be due to the spontaneous resolution of each attack over seconds to a few minutes, rather than any beneficial therapeutic effect. The exceptions to this are 3 patients: one with concomitant cluster headache, one in whom there was a minimal effect, and one in whom the oxygen changed the quality of the pain from sharp to burning, although this patient also suffered from constant background pain which may have confused the situation somewhat.

10.3 Oxygen and GTN triggering

Nitric oxide has been shown to play a pivotal role in primary headache syndromes. Both migraine and cluster headache attacks are inducible by nitric oxide donors such as nitroglycerin (Ekbom, 1968; Olesen et al., 1995; Sances et al., 2004). Nitric oxide is thought to act as an inhibitor of cytochrome oxidase (Decking et al., 2001), and increases the cell's requirement for oxygen for cellular respiration (Cooper et al., 2003).

It has been proposed that migraine is a disorder of energy metabolism in the brain, reviewed by (Tepper et al., 2001), and mitochondrial impairment has been shown in proton spectroscopy in migraine and cluster headache (Lodi et al., 1997). Mitochondrial dysfunction has also been suggested by the response by migraine patients to riboflavin prophylaxis (Schoenen et al., 1994), the nitric-oxide scavenger hydroxycobalamin (van

der Kuy et al., 2002) and Coenzyme Q (Sandor et al., 2005a). These all point to the suggestion that abnormalities in energy metabolism predispose migraine and cluster headache sufferers to develop an attack under conditions of increased energy demand, and that treatment with protagonists of the cellular respiratory cycle, such as the aforementioned vitamins, may be effective by reducing the oxidative stress (Montagna, 2002). Oxygen may also exert a therapeutic effect reducing oxidative stress and promoting cellular respiration.

The current results showed that sublingual nitroglycerin did not trigger an attack in 83% of SUNCT and both SUNA patients. In all of these patients, including the one SUNCT patient in whom GTN triggered an attack, oxygen had no effect in aborting their attacks. Although these numbers are small, they indicate that SUNCT and SUNA are not precipitated by nitric-oxide donors, unlike migraine and CH. Therefore the lack of response to oxygen is unsurprising. Furthermore any response to oxygen at a cellular level may be missed as the attacks being of short duration will end before they can be terminated by inhaled oxygen.

10.4 Short-term preventive medications

Indomethacin

Oral indomethacin in doses up to 300mg a day has been reported as mainly ineffective (Gardella et al., 2001; Hunt et al., 2002; Koseoglu et al., 2005; Matharu et al., 2004b; Narbone et al., 2005; Prakash and Lo, 2004; Rossi et al., 2003; Volcy et al., 2005). The *Indotest* (Antonaci et al., 1998) and modified *Indotest* (double-blind, placebo-controlled, intramuscular indomethacin 100mg) have also been found to be negative (Matharu et al., 2004b).

In this study, the modified *Indotest* was universally minimally effective or negative in all SUNCT and SUNA patients who underwent it, even in those patients with longer-lasting attacks or constant background pain, in whom the differential diagnosis would be paroxysmal hemicrania and hemicrania continua respectively. It is therefore proposed

that a diagnostic indicator for SUNCT would be a negative response to the modified Indotest. A positive response to an indomethacin challenge in each patient with suspected SUNCT would negate the diagnosis of SUNCT, and point towards either HC or PH.

Oral indomethacin is also ineffective in 89% of SUNCT and SUNA. In the two patients who reported a moderate effect, the fact that neither patient reported an absolute response to indomethacin as is characteristic of paroxysmal hemicrania (Antonaci et al., 1998), would suggest that indomethacin is generally not a useful treatment in SUNCT/SUNA.

Lidocaine

In this study, all patients receiving intravenous lidocaine reported some relief to total abolition of their symptoms, the longest pain-free period being 3 weeks in a patient with chronic SUNCT, 12 weeks painfree in chronic SUNA, and 6 months painfree in a patient with episodic SUNCT. In the case of episodic SUNCT it could be argued that the painfree period was just that the patient was in remission between her bouts of pain; however her usual remission period was only 4 weeks.

Intravenous lidocaine has been reported previously in 4 patients with SUNCT, providing them with pain-free times of up to 12 hours (Matharu et al., 2004b), and in a further case with pain relief of an unknown duration (Shiiba et al., 2005). Lidocaine has also been used in 2 patients with cluster headache (Sakamoto et al., 2005).

Intravenous lidocaine has been demonstrated to provide effective analgesia in a variety of acute and chronic pain states (Galer et al., 1993; Mao and Chen, 2000). It has been reported to be effective in several headache syndromes including trigeminal neuralgia (Kugelberg, 1959), chronic migraine (Kaube et al., 1994) and cluster headache (Maciewicz, 1988). It has been proposed as treatment for chronic daily headache including analgesic rebound headache (Hand and Stark, 2000), and was found to be helpful in acute or chronic migraine or status migrainosus in a retrospective study (Jauslin et al., 1991), although a brief infusion at 1mg/kg/minute did not prove effective in migraine in one trial (Reutens et al., 1991). Pareja and colleagues have reported that

intravenous lidocaine 100 mg bolus followed by 4 mg/minute over 48 hours was ineffective when administered to two patients with SUNCT (Pareja et al., 1995), although these were only given for a duration of 48 hours. Since then, lidocaine has been found to be useful in two retrospective series of 71 patients (Williams and Stark, 2003), and 12 patients (Siow, 2005), most of whom had chronic migraine, and in case reports of cluster headache and SUNCT (Sakamoto et al., 2005). In this study intravenous lidocaine was highly effective in patients with SUNCT and SUNA. The range of response varies from reduction of severity or frequency of the attacks for the duration of the infusion, to a pain free state lasting up to 6 months. Remarkably there are no cases encountered of SUNCT that have not responded to some extent to intravenous lidocaine.

Intravenous lidocaine, which is an amide local anaesthetic and anti-arrhythmic agent, was first used in 1961 for post-operative pain treatment (Bartlett and Hutserani, 1961). It is often used for the treatment of peripheral neuropathic pain (Mao and Chen, 2000). It blocks peripheral and central sodium channels (Nagy and Woolf, 1996; Woolf and Wiesenfeld-Hallin, 1985) and selectively inhibits abnormal ectopic neuronal discharges (Devor et al., 1993) but without blocking normal nerve conduction in animal models (Devor et al., 1992). The abnormal ectopic discharges may be explained by increased numbers of sodium channels which have been found in the demyelinated brain lesions of human multiple sclerosis and in demyelinated central axons of rodents (England et al., 1996), and the NaV₁ channel subtype in peripheral nerve injury, which is alleviated both by the lidocaine derivative mexiletene and lamotrigine (Lindia et al., 2005).

Neuropathic pain states such as hyperalgesia and allodynia respond to systemic lidocaine (Chaplan et al., 1995; Jasmin et al., 1998). In clinical studies, intravenous lidocaine (3mg/kg over 3 minutes followed by a continuous infusion of 4mg/kg for 60 minutes) was effective in treating thalamic pain, trigeminal neuralgia, and phantom limb pain, but had no benefit on peripheral (nociceptive) pain such as pressure-cuff induced ischaemic pain (Boas et al., 1982). A meta-analysis of 16 randomised, double-blind, placebo-controlled trials showed beneficial effect of intravenous lidocaine (1-5mg/kg) compared to placebo in chronic neuropathic pain such as diabetic neuropathy, postherpetic

neuralgia, post-traumatic peripheral neuropathy, cancer-related neuropathy, and central/mixed neuropathy such as that due to stroke, amputation and spinal cord injury (Challapalli et al., 2005).

The effectiveness of lidocaine in SUNCT may be due to the neuralgiform characteristics of the attacks. SUNCT differs from other primary headache syndromes and TACs by the ability to trigger attacks from cutaneous stimuli such as touching the face. It could therefore be suggested that lidocaine acts on the trigeminal nerve in the periphery or at the level of the trigeminal ganglion in order to block nociceptive transmission. However this would not explain why it had a good effect on those patients whose attacks were mainly or all spontaneous (Patients #2, 7, 12, 22, 27, 34, 36, 57 and 3 out of 4 SUNA patients). The beneficial effects of lidocaine in other primary headache syndromes such as migraine may be due to the development of central sensitisation (Burstein, 2001; Burstein et al., 1998), as manifested by cutaneous allodynia and intracranial hypersensitivity (Yamamura et al., 1999). Central sensitization may be mediated by sodium channel-related ectopic discharge from chronically injured neurons in the spinothalamocortical pathways (Max and Hagen, 2000). A study of intravenous lidocaine (5mg/kg over 30 minutes) in allodynia and hyperalgesia in central pain syndromes suggested that lidocaine has a central as well as a peripheral effect (Attal et al., 2000). This in combination with the observation that three drugs that reduce central pain- amitriptyline, lamotrigine and lidocaine- all block sodium channels, raises the possibility that this is one of their mechanisms of action in primary headache syndromes. However we have reported an overwhelming lack of response to amitriptyline in SUNCT and SUNA, which is borne out in the literature (Matharu et al., 2003a; Matharu et al., 2004b; Pareja et al., 1995), except when used in combination with other drugs such as gabapentin, topiramate, carbamazepine and lamotrigine.

The apparent discrepancy between this study's findings and those of Pareja et al (Pareja et al., 1995) may be due to a number of factors. First, the plasma level of lidocaine (2-5 µg/ml) appears to be the determinant of effectiveness of systemic lidocaine, regardless of the route of administration (Devulder et al., 1993), and this was not measured in either

study. Secondly, the rate of intravenous infusion appears to be a determinant factor of the outcomes (Chaplan et al., 1995), although these were comparable between the two studies. Third, the duration of the infusion differs between a bolus injection (Maciewicz, 1988), to 48 hours (Pareja et al., 1995), to up to 7 days (in our study), to a maximum of 17 days (Williams and Stark, 2003). Other factors include the number of patients studied in each trial, and differing endpoints for reporting effectiveness, such as reduction in attack frequency or complete abolition of attacks.

Occasionally, patients with SUNCT syndrome experiencing severe exacerbations with frequent, easily triggered, high-intensity pain attacks are encountered (Montes et al., 2001; Pareja et al., 1996a). In this situation, acute interventions are needed because the patients are severely affected and may not be able to eat or drink because these actions trigger attacks. This report draws attention to the possibility of utilising intravenous lidocaine in this situation to ameliorate the attacks temporarily while conventional therapy is being optimised. One great advantage of a successful response to lidocaine infusion is that the patient may be rendered pain free for up to many weeks after the infusion, which has been noted in animal models with prolonged reduction of tactile allodynia far beyond the pharmacological half-life of lidocaine (Chaplan et al., 1995; Sinnott et al., 1999). This allows a period of time where the patient can be drug free, or for titration of preventive medications. Appendix 3 outlines the protocol we employ when administering intravenous lidocaine. Treatment with intravenous lidocaine is associated with significant side effects, especially when high doses are utilised (Ferrante et al., 1996; Rowbotham et al., 1991; Wallace et al., 1996). As it mediates its effect through blockade of sodium channels, including those in the heart, brain and peripheral nerve, it may cause adverse effects at each site, including pro-arrhythmic effects, cognitive impairment and neuropsychiatric side effects, dizziness, nausea, and diarrhoea. For this reason, it is imperative to monitor the patient carefully for adverse effects.

Therefore it is suggested that infusion of intravenous lidocaine, up to 3.5mg/kg/hour, has both diagnostic and therapeutic use in SUNCT/SUNA. From a diagnostic point of view, the lack of response to intramuscular indomethacin, combined with a reduction of attacks

on intravenous lidocaine, would point strongly towards a diagnosis of SUNCT/SUNA. In terms of therapy, many patients especially with the chronic forms have not had a significant period of time free of pain, or have required preventive medications which may cause side effects. The prospect of an infusion for a few days which can render patients pain free (and therefore free of preventive drugs) for up to 6 months at a time is very attractive for this severely painful and otherwise undermanaged condition.

10.5 Preventive Medications

10.5.1 Lamotrigine

Lamotrigine is a relatively new anticonvulsant drug effective in partial and generalised tonic clonic seizures. It blocks voltage-sensitive sodium channels, thereby stabilising the neuronal membrane and inhibiting the release of excitatory neurotransmitters such as glutamate and aspartate. It has been shown to share broadly similar antinociceptive effects with lidocaine in different animal models of neuropathic pain (Erichsen et al., 2003).

In randomised trials, it has been used to a good effect in 11 out of 13 patients with TN (at 400mg/day) (Zakrzewska et al., 1997) and has also been shown to be beneficial in various neuropathic pain syndromes such as painful HIV-associated neuropathy (300mg/day) (Simpson et al., 2000) and central post-stroke pain (200mg/day) (Vestergaard et al., 2001), although it was not better than placebo at 200mg/day in a trial of various neuropathic conditions (McCleane, 1999). It was first used in 37 patients with migraine at 200mg/day but was no better than placebo in preventing the migraine attacks (Steiner et al., 1997a). In subsequent studies at 100mg/day, it was shown to be better than placebo in reducing aura symptoms in 15 patients (Lampl et al., 1999), and in patients with high frequency of migraine with aura (D'Andrea et al., 1999b). It was subsequently shown to reduce migraine attacks in those patients with aura, in an uncontrolled trial (Lampl et al., 2005). In terms of other primary headache syndromes, lamotrigine has been shown to be useful at mean doses of 250 mg/day in TN and trigeminal dysaesthesia but

not CH or migraine in open-label trials (Delvaux and Schoenen, 2001). Interestingly it has been recently reported as ineffective in animal models of trigeminal neuralgia, whereas gabapentin was effective (Christensen et al., 2001).

Lamotrigine inhibits voltage-gated sodium channel conductance, thus inhibiting the excitatory neurotransmitters glutamate and aspartate, and stabilising the neuronal membrane (Cheung et al., 1992; Thomas, 1997). This action is shared by carbamazepine and phenytoin, although phenytoin has not been shown to have a beneficial effect in SUNCT; on the other hand carbamazepine has been reported to have some effect (Matharu et al., 2003a; Matharu et al., 2004b), but only 39% of patients in this study reported it to be effective, as opposed to 68% of SUNCT patients in whom there was a moderate to good effect of lamotrigine. It has been recently shown that lamotrigine also modulates calcium currents and the transient potassium outward current, presumably in a voltage-gated fashion (Grunze et al., 1998). This may be an additional method of action of lamotrigine which may be of benefit in SUNCT. It is interesting to note that it inhibits N-type channels (Wang et al., 1998), as opposed to L-type calcium channels which are antagonised by verapamil (Spedding and Paoletti, 1992). This may explain why lamotrigine has success in SUNCT and SUNA, whereas verapamil is either ineffective, or makes the attacks worse (Jimenez-Huete et al., 2002; May et al., 1999b).

Recently, lamotrigine given in an open-label manner at doses up to 300mg a day has been reported to be highly efficacious in 10 patients with SUNCT (D'Andrea et al., 1999a; D'Andrea et al., 2001; Gutierrez-Garcia, 2002; Leone et al., 2000b; Malik et al., 2002), although it has been reported as ineffective in 4 patients (Black and Dodick, 2002; Matharu et al., 2004b; Sprenger et al., 2005), and ineffective at 400mg a day in a patient with SUNCT related to trigeminal nerve compression (Koseoglu et al., 2005).

Sixty-eight per cent of SUNCT patients in this study reported a good or moderate effect with lamotrigine, at doses of 50-400mg daily. Of these, 9 had a good effect in that their attacks were completely suppressed, and 8 had a moderate effect either with lamotrigine

alone or in combination with other neuromodulatory drugs such as gabapentin, amitriptyline, topiramate, and carbamazepine.

Problems with lamotrigine include a skin reaction which may progress to Stevens-Johnson syndrome, and this necessitated the cessation of lamotrigine in at least one patient in the literature (Rossi et al., 2003). A sizeable proportion of our cohort (6 patients) who tried lamotrigine had to stop it, often at suboptimal doses, due to side effects, such as anaphylactic reaction (4 patients), skin rash (4 patients reported this but only 2 patients actually stopped the lamotrigine because of it), arthralgia (1 patient), and suppressing the attacks but making the patient's migraine worse (1 patient). In one patient the lamotrigine actually made the SUNCT attacks worse: it appears that this is the only case of lamotrigine worsening SUNCT attacks.

In the double-blind placebo-controlled study of lamotrigine in SUNCT, of the four patients who were randomised to the trial, one withdrew in the first two weeks because his pain was so severe on withdrawal of his previous preventive (carbamazepine 1600mg daily), and he did not want to take a placebo for a few months. Two patients completed both arms of the study, but did not complete the diaries. However they both reported that neither treatment had any beneficial effect on their attacks. The patient who did complete the trial had no beneficial effect with either lamotrigine or placebo; indeed both treatments increased both the attack frequency and attack load from baseline.

The disappointing results in the placebo-controlled trial may be due to a number of reasons. The first is that the patients who agreed to take part in the trial were self-selecting in terms of chronic SUNCT/SUNA which had not responded to other medications; thus their individual disease may have been more refractory to treatment than other SUNCT/SUNA patients. The second is that the dose of lamotrigine may not have been high enough at 200mg daily. Some of our patients taking lamotrigine in an open-label fashion required doses up to 400mg for a beneficial effect. The third reason is that the diary recording was inaccurate. It is disappointing that 2 patients defaulted on completion of the diaries; however with at least 20 and up to many hundreds of attacks a

day, some patients find it arduous to complete the diaries at this frequency. In the patient whose attacks were worsened on both treatments, it may be that he unwittingly recorded a greater proportion of his attacks whilst on the treatments. It may also be that lamotrigine may have a differential effect on triggered and spontaneous attacks, in that it may suppress the spontaneous attacks but attacks could still be triggered by cutaneous stimuli. Of note, all 3 patients had attacks which were at least 50% triggered.

The open-label study showed a discrepancy between SUNCT (with 68% reporting moderate or good effects) and SUNA, where only one out of the 4 (25%) reported a good effect with lamotrigine. This may reflect either a difference between SUNCT and SUNA as disease states, such that SUNCT responds better to lamotrigine than SUNA; otherwise it could be a feature of the small number of SUNA patients who tried it.

Definitive answers would be obtained from placebo-controlled double-blind trials, although the current experience implies that these trials are impossible due to the rarity of the two syndromes, the incidence of side effects, and the reluctance of patients to take a placebo for a period of months at a time. The latter factor alone gives an indication as to the extraordinary degree of morbidity from such short-lasting attacks, both in terms of the severity of the pain and the debilitating effect of many attacks daily; that most patients refused to take a placebo when the active treatment was available.

Therefore, in the absence of double-blind placebo-controlled trials, the use of lamotrigine is recommended as a primary preventive agent in SUNCT/SUNA, as long as side effects do not intervene. The dosing regimen for lamotrigine treatment in SUNCT/SUNA is the same as in the double-blinded trial.

10.5.2 Topiramate

These results show a beneficial response of topiramate in SUNCT in two patients; one with complete cessation of his attacks, and one with reduction of his attack load in

minutes per day. In the other three patients no beneficial response was seen with topiramate, according to the predetermined endpoints of the study.

Two patients had a placebo response. One (#47) had cessation of his attacks on placebo. However this patient had episodic SUNCT so it is possible that his attacks went into spontaneous remission, and this effect was wrongly ascribed to the tablets. The high success rate of placebo has been noted in a negative trial of valproate in episodic cluster headache with the same problem (El Amrani et al., 2002b).

The second patient (#21) noted a reduction in his headache load on placebo. These headaches were episodes of pain lasting up to 720 minutes each, and were probably prolonged attacks of SUNCT which occurred in groups of stabs. Each one was recorded by the patient as a single headache, although there may be an argument for each one to be recorded as multiple single stabs or groups of stabs. In this case it would be very difficult for the patient to record accurately the number of attacks he experienced; and it would also make a great difference to the attack frequency per day. On disregarding these long headache episodes and concentrating on the measurable SUNCT attacks, he had increased attack frequency on both topiramate and placebo, although less so on topiramate (+19%) than placebo (+52%). However in comparing the attack load, there was a large increase on placebo (+178%), as compared to a significant decrease on TPM (-71%), which would indicate that topiramate was effective in reducing the number of minutes of pain per day in terms of SUNCT attacks. It is therefore useful to employ a system of co-primary endpoints when assessing the efficacy of preventive medications.

In the open-label trial in SUNCT of topiramate at doses up to 400mg daily, there was a moderate or good response in 52% of patients, one of whom combined the topiramate with lamotrigine for an optimal effect. One SUNA patient took topiramate 800mg daily, which had a good effect on her migraine but no effect at all on her SUNA.

Topiramate has been reported to be effective in 6 SUNCT patients at doses up to 300mg daily (Kuhn et al., 2005; Matharu et al., 2002; Matharu et al., 2004b; Rossi et al., 2003), and ineffective in three patients (Black and Dodick, 2002; Koseoglu et al., 2005).

Problems with topiramate included side effects, which in some patients necessitated the cessation of the drug even though it had a good effect on the attacks, and in other patients the topiramate was withdrawn before an optimal therapeutic dose could be achieved.

Topiramate is known to cause the side effects which our patients experienced, although they are usually found at higher doses and in faster regimes of escalation than those used in our practice (Ojemann et al., 2001). In SUNCT, two patients reported mild hypersomnolence at doses of 75 and 300mg a day respectively, but as they were rendered pain free and the headaches recurred on reducing the dose, they maintained the topiramate treatment (Matharu et al., 2004b; Rossi et al., 2003).

Other known side effects of topiramate include commonly somnolence, paraesthesiae, diminished appetite, nausea, diarrhoea, weight loss, and dysgeusia (Silberstein, 2005).

Central nervous system adverse events included somnolence, insomnia, memory difficulty, language problems, concentration difficulty, mood problems and anxiety (Silberstein, 2005). Additionally, renal calculi and paraesthesiae occur rarely (Rosenfeld, 1997), attributed to weak carbonic anhydrase inhibition by topiramate. It is suggested that starting at low doses, once or twice daily, and making small increments thereafter can minimize side effects; such was the case in a group of cluster headache patients (Wheeler and Carrazana, 1999).

Topiramate exhibits potent antiepileptic action in animal and clinical models (Abou-Khalil, 2000; DeLorenzo et al., 2000; Stephen et al., 2000; Yen et al., 2000). It has multiple mechanisms of action (Rosenfeld, 1997). They include modulating voltage-gated sodium ion channels, blocking excitatory glutamate receptors, modulating voltage-gated calcium ion channels, inhibiting carbonic anhydrase, and enhancement of inhibitory GABA-mediated chloride influx through GABA_A receptors (Chong and Libretto, 2003). Indeed animal models (Akerman and Goadsby, 2005; Storer and Goadsby, 2004) have

shown that topiramate inhibits trigeminovascular activation, which is a surrogate marker for headache, and may explain the site of its anti-migraine action. Topiramate has been demonstrated to increase human cerebral GABA concentrations in healthy subjects and patients with epilepsy using nuclear magnetic resonance spectroscopy (Kuzniecky et al., 1998; Petroff et al., 2001). This is similar to the mechanism of action of valproate (Fariello, 1995), upon which its action in migraine (Hering and Kuritzky, 1992; Jensen et al., 1994) and cluster headache (Hering and Kuritzky, 1989) may be based.

Methodological and Analytical Issues

The primary endpoint in analysis was the reduction of frequency of attacks, as measure in attacks per day. It was originally decided to perform a group analysis using multi-level, multi-variate analysis (Snijders, 1999), using the software that has been developed by the Multi-level Project, MlwiN (available at <http://www.ioe.ac.uk/multilevel>), as has been used in previous studies (Levy et al., 2005; van Vliet et al., 2003a).

However the large inter-patient range of numbers of attacks per day (from 7 to 140 in this series) would make statistical analysis rather difficult in a group setting.

The concept of 'attack load' has been introduced in Chapter 5.11, in order to account for the large variation in duration and frequency of attacks, both between patients and also in patients who experience longer attacks as a group of smaller stab-attacks. This phenomenon occurred in 2 patients in this series (#21 and #34). Therefore the concept of 'attack load' was measured, that is, number of minutes of pain per day. The 'attack load' was analysed both for the SUNCT attacks for which the trial was initially set out, and also for 'total headache attack load', which included other head pains such as dull background headaches which may have been a feature of the SUNCT (Cohen et al., 2005b).

Another issue is the dose given. The patients in this trial received a maximum dose of 100mg a day, yet in other trials and clinical work the dose has been increased to 300-400mg daily (Cohen et al., 2005c; Matharu et al., 2002; Matharu et al., 2004b; Rossi et al., 2003). It may be that a higher dose of topiramate would have a greater beneficial

effect in some patients, although there has been a recent report of no observed increase in efficacy between 100 and 200 mg per day of topiramate in migraine prevention (Silberstein et al., 2004), and there was a higher incidence of adverse effects at the higher dose. Indeed it has been noted that patients at 200mg of topiramate had no response as opposed to patients in the same series on smaller doses (Leone et al., 2003a).

In summary, topiramate had a good effect in 2 of 5 patients as compared to placebo. In two patients there was no effect at all, and one patient had a marked placebo response which could be attributed to spontaneous remission of his attacks. The methodological shortcomings of the study have been discussed, and it is felt on balance that these results would not persuade us to reject topiramate as a treatment for SUNCT. SUNCT has until recently been thought of as an untreatable condition, and with a 40% success rate in this placebo-controlled trial and 52% success rate in an open-label study, the use of topiramate is still advised in SUNCT. Patients with a previous history of renal stones, glaucoma, depression, and those who are underweight, should not be offered topiramate as a first-choice agent, in case of developing known side effects.

10.5.3 Gabapentin

Gabapentin was first used in trigeminal neuralgia in two patients at doses up to 2400mg daily with good effect (Sist et al., 1997), and has since been shown to be effective in open-label studies in idiopathic TN (Valzania, 1998) and in TN associated with multiple sclerosis (Khan, 1998; Solaro et al., 1998). It has also been effective on open-label in TN in combination with lamotrigine or carbamazepine, at mean doses of CBZ 400 mg and GBP 850 mg daily; or LTG 150 mg and GBP 780 mg daily in 11 patients with TN and MS (Solaro et al., 2000). It has been shown to be effective in animal models of trigeminal neuropathic pain as compared to lamotrigine (Christensen et al., 2001).

Gabapentin has been used with good effect in migraine (Di Trapani et al., 2000; Mathew et al., 2001), cluster headache (Ahmed, 2000; Tay et al., 2001), and trigeminal neuralgia (Cheshire, 2002). SUNCT has been shown to respond to gabapentin, with complete

suppression of attacks in three of nine patients treated with 800 to 2700 mg daily (Graff-Radford, 2000; Hunt et al., 2002; Porta-Etessam et al., 2002), and minimally effective in one patient with SUNA at an unknown dose (Volcy et al., 2005). However it has been reported as completely ineffective in 9 patients (Koseoglu et al., 2005; Malik et al., 2002; Matharu et al., 2003a; Matharu et al., 2004b), although in 1 patient this was SUNCT secondary to compression of the trigeminal nerve (Koseoglu et al., 2005).

The mechanism of action of gabapentin is not fully understood. It is structurally related to the neurotransmitter γ - amino butyric acid (GABA), and it does not interact with GABA receptors or GABA metabolism, it increases brain GABA in animals (Loscher et al., 1991) and humans with epilepsy (Petroff et al., 2000; Petroff et al., 1996). It has also been shown to bind to the α_2 - δ subunit of voltage-gated calcium channels (Gee et al., 1996), and this plays an important role in the maintenance of mechanical hypersensitivity in animal models of neuropathic pain (Field et al., 2000). These have later been found to be L-type and P/Q-type calcium channels (Oka et al., 2003). Gabapentin attenuates the noxious stimulus-induced increases in spinal glutamate release in neuropathic rats *in vivo* (Coderre et al., 2005), and in trigeminal slices of rats in whom tactile allodynia was induced (Maneuf et al., 2004; Maneuf et al., 2001).

This series shows complete resolution of attacks in only one patient (5%), and with a moderate effect in 9 SUNCT patients (41%) and 3 SUNA patients (60%), either alone or in combination with other drugs such as lamotrigine, carbamazepine or topiramate. It is interesting to note that in one SUNCT patient with MS (#52) it had a good effect at 1600mg for 3 months before wearing off, and subsequently had a mild effect at 3000mg when combined with lamotrigine 400mg, where other medications were unsuccessful for this patient (amitriptyline 100mg, carbamazepine at unknown dose).

Interestingly in this series gabapentin was effective in 60% of SUNA but only 45% of SUNCT patients. It may be that the SUNA patients respond more in a pattern of hypersensitivity and stimulus-induced pain; although the argument against this is that our phenotype study shows that most of the SUNA patients (67%) had entirely spontaneous

attacks which could not be triggered. In only 1 SUNA patient (#SUNA59) who responded to gabapentin were the attacks triggerable. It is also possible that due to the small numbers of patients, the difference between SUNCT and SUNA is not significant. Most striking is the beneficial effect of adding gabapentin to other neuromodulatory drugs such as lamotrigine, carbamazepine and amitriptyline. Gabapentin was initially used as an add-on therapy for epileptic seizures (Anhut et al., 1994; Morrell et al., 2000), although its efficacy as monotherapy for complex partial seizures has also been recognised (Bergey et al., 1997). It acts synergistically with other neuromodulators such as carbamazepine, lamotrigine, valproate, phenytoin and phenobarbital in models of epilepsy (Borowicz et al., 2002). In terms of pain, it has an additive analgesic effect with amitriptyline in animal models (Heughan and Sawynok, 2002), and is useful combined with either lamotrigine or carbamazepine for trigeminal neuralgia in multiple sclerosis (Solaro et al., 2000). Therefore it may be the synergistic effect of gabapentin with other anti-epileptic drugs which is successful in the treatment of neuralgiform-type pain.

This study shows complete resolution of attacks in only one patient (5%), and with a moderate effect in 9 SUNCT patients (41%) and 3 SUNA patients (60%), either alone or in combination with other drugs such as lamotrigine, carbamazepine or amitriptyline. It is therefore recommended that gabapentin be used as a second-line agent in SUNCT, possibly in combination with another neuromodulatory drug. It may prove a first-line agent in SUNA given its 60% response rate as monotherapy.

10.5.4 Carbamazepine

Carbamazepine has been a mainstay of treatment in trigeminal neuralgia (Backonja and Serra, 2004), and has also been reported as having a good or partial effect in SUNCT at doses up to 900mg a day (Matharu et al., 2003a; Matharu et al., 2004b), especially when used in combination with naloxone, verapamil and lithium (Sabatowski et al., 2001); prednisolone (Calvo et al., 2004; Gardella et al., 2001; Montes et al., 2001), topiramate (Matharu et al., 2004b), and indomethacin (Prakash and Lo, 2004). However there are some reports of carbamazepine having no effect at doses of 100-1200mg a day (Cohen et

al., 2004; Koseoglu et al., 2005; Rossi et al., 2003), and only a mild effect at 1600mg a day (Gantenbein and Goadsby, 2005).

In this case series, 14 of the 36 SUNCT patients (39%) reported a moderate or good effect with carbamazepine, although only 4 of these (11%) actually reported complete cessation of their attacks. Only 1 SUNA patient (20%) reported a moderate effect; in the rest there was no beneficial effect.

10.5.5 Valproate

Valproate, which is used commonly in migraine (Hering and Steiner, 1994; Jensen et al., 1994), has been ineffective in doses up to 2000 mg a day in eight patients with SUNCT, was partially effective in one, and transiently had a good effect when combined with nortriptyline and prednisolone in another patient (Matharu et al., 2004b; Pareja et al., 1995; Sesso, 2001). It was ineffective in a patient with SUNA at 15mg/kg/day (375mg/day) (Volcy et al., 2005). This study found no effect of valproate in any of the 9 SUNCT or 1 SUNA patients who tried it.

10.5.6 Other anticonvulsants

Other anticonvulsants tried in our SUNCT cohort were oxcarbazepine, phenytoin, clonazepam, leviteracetam; all with no beneficial effect. The leviteracetam made the attacks worse in the SUNCT patient who took it. Pregabalin had a moderate effect in 2 SUNCT patients (although unsustained in one), and no effect in one SUNA patient.

These drugs have been used in the past as follows, with little or no effect in SUNCT: oxcarbazepine (2400mg/day (Sprenger et al., 2005)) (1800mg/day in the patient with SUNCT associated with compression of the trigeminal nerve) (Koseoglu et al., 2005), baclofen, both alone and in combination with carbamazepine (Calvo et al., 2004), and clonazepam (Matharu et al., 2004b).

Phenytoin has been tried in 10 patients and was reported to be mostly ineffective (Malik et al., 2002; Pareja et al., 1995). It has been used in combination with carbamazepine, which had no beneficial effect but caused ataxia (Matharu et al., 2004b).

The use of pregabalin has not been previously reported in SUNCT or SUNA. It has been used with good effect in neuropathic pain and post-herpetic neuralgia (Freynhagen et al., 2005; Sabatowski et al., 2004), and also reduced sleep disturbances (Sabatowski et al., 2004). Pregabalin is known to alter sleep architecture by enhancing non-rapid eye movement sleep in rats and humans (Hindmarch, 2001; Kubota et al., 2001). Cluster headache and other hypothalamically-driven headaches are known to have distorted sleep architecture (Cohen and Kaube, 2005), and it is possible that pregabalin exerts its effect in SUNCT via this shared mechanism. This study reports 2 cases of SUNCT with moderate response to pregabalin, although in one patient the duration of its effect was limited. Pregabalin had no effect in the SUNA case.

10.5.7 Amitriptyline and tricyclic antidepressants

Amitriptyline and other tricyclic antidepressants are commonly used in the treatment of migraine (Couch et al., 1976; Punay and Couch, 2003; Ziegler et al., 1987), neuropathic pain (McQuay et al., 1996; Sindrup and Jensen, 1999) and atypical facial pain (Lascelles, 1966), but there are no randomised controlled trials of amitriptyline in trigeminal neuralgia. It is interesting to note that a total of 31 of the cohort had been given amitriptyline in doses up to 150 mg a day, and only one patient reported a moderate benefit but with side effects of a dry mouth and drowsiness. Other patients have taken dothiepin and lofepramine with no effect on their attacks. One patient also took the antidepressant mirtazapine, with no beneficial effect on his attacks. It therefore seems that amitriptyline and tricyclic antidepressants are unlikely to produce major beneficial effects in SUNCT or SUNA. This further contributes to the separation of SUNCT/SUNA in terms of pathophysiology from other facial pains.

10.5.8 Melatonin

The hypothalamus is known to regulate circadian rhythms, through the suprachiasmatic nucleus (SCN) (Ralph et al., 1990), with information about the level of ambient light through the retino-hypothalamic tract (Reppert and Weaver, 2002). Photoc information relayed from the SCN to the pineal gland is closely reflected there in the secretion of melatonin (Brzezinski, 1997; Utiger, 1992). Melatonin secretion is known to be abnormal in cluster headache (Chazot et al., 1984; Leone and Bussone, 1993; Leone et al., 1995; Waldenlind et al., 1987), and has had some success as a therapeutic agent in cluster headache (Leone et al., 1996; Peres and Rozen, 2001). In the light of these findings, and on the basis that SUNCT/SUNA possibly share a common hypothalamic pathophysiology with CH, one SUNCT patient took melatonin with a moderate response, although interestingly it had little to no effect in the SUNA patients. This may be because SUNA patients generally are more refractory to medications than SUNCT patients, or that there is different hypothalamic activation between SUNCT and SUNA. Further SUNCT/SUNA patients may be offered melatonin as a relatively side-effect-free alternative to other preventive therapies, although with only one patient having a moderate effect, it may be premature to suggest that melatonin has a definitive effect in SUNCT.

10.5.9 Corticosteroids

Corticosteroids, particularly prednisolone, are used in the treatment of cluster headache (Antonaci et al., 2005; Couch and Ziegler, 1978; Kudrow, 1980), and there have been some benefits reported in SUNCT (Matharu et al., 2003a), and also at doses of 40-60mg/day in combination with carbamazepine (Calvo et al., 2004; Gardella et al., 2001; Montes et al., 2001). In this study, one patient reported a mild benefit at 80mg a day of prednisolone (#9), and another reported that 50mg a day of prednisolone reduced the frequency of his attacks (#20). However the latter patient had SUNCT secondary to a pituitary prolactinoma, and so the corticosteroids may have been acting on his pituitary-adrenal axis rather than on the headache attacks themselves. The rest of the SUNCT and

all SUNA patients reported no benefit on prednisolone at doses up to 60mg, and there is another report showing no benefit of 60mg prednisolone for 1 month (Rossi et al., 2003).

10.5.10 Verapamil and Lithium

Verapamil at high doses (up to 960mg/day), and lithium (to a therapeutic range of 0.8-1.1 $\mu\text{mol/l}$) are usually used in cluster headache (Bussone et al., 1990; Ekbom, 1981; Leone et al., 2000a), and have had little or no reported effect in SUNCT (Gardella et al., 2001; Matharu et al., 2003a; Rossi et al., 2003). Verapamil made the attacks worse in some cases (Jimenez-Huete et al., 2002; May et al., 1999b), except in one recent case where verapamil at doses of 480-960mg a day abolished attacks in a patient with SUNCT and an ischaemic lesion in the posterior fossa (Narbone et al., 2005). Lithium and verapamil are both known to accumulate in the hypothalamus (Bussone et al., 2003; Dodick et al., 2003), which probably plays a role in the generation of both CH and SUNCT attacks, so it might be expected for them to have some beneficial effect in SUNCT. In nine SUNCT patients who took verapamil, one patient had a mild effect but this was not enough to control his attacks. One SUNA patient also had cluster headache, and the verapamil helped both for his cluster headache and also to reduce the frequency of his SUNCT attacks. There is as yet no firm evidence of the beneficial effect of lithium.

10.5.11 Other medications

Analgesics and non-steroidal anti-inflammatory drugs (NSAIDS)

Simple analgesics (paracetamol, aspirin), opiates (morphine, tramadol, buprenorphine, dihydrocodeine), and combination analgesics (paracetamol/codeine, hydrocodone/acetaminophen), have all been reported as ineffective (Malik et al., 2002; Matharu et al., 2003a; Matharu et al., 2004b; Putzki et al., 2005). NSAIDs, including ibuprofen, piroxicam, naproxen, ketoprofen, aspirin, mefenamic acid, are ineffective in the treatment of SUNCT and SUNA (Matharu et al., 2003a; Matharu et al., 2004b; Rossi et al., 2003; Volcy et al., 2005).

This study adds a further list of NSAIDs, cyclooxygenase-2 inhibitors, simple and compound analgesics, and opiate analgesics, which are ineffective in SUNCT and SUNA. These include aspirin, aspirin/caffeine preparations, ibuprofen, diclofenac, paracetamol/opiate preparations, celecoxib and rofecoxib.

Serotonergic agonists and antagonists

Methysergide and pizotifen had no effect in the SUNCT patients in this study, and this corresponds to their ineffectiveness as reported in the literature (Goadsby and Lipton, 1997; Matharu et al., 2004b; Pareja et al., 1995). Likewise selective serotonin reuptake inhibitors (SSRIs) have been used in SUNCT in the past, including sertraline (100mg/day) (Koseoglu et al., 2005) and fluoxetine (20mg/day) (Matharu et al., 2004b), with no effect.

Adrenoreceptor blockers

Beta-blockers such as propranolol, and alpha-blockers such as clonidine, have been reported to be ineffective in SUNCT (Matharu et al., 2003a), and as such their use has not been recorded since. This database adds a further 6 patients with propranolol up to 160 mg a day, which had no effect on their SUNCT or SUNA.

10.6 Surgery

Several surgical approaches have been attempted for the treatment of SUNCT syndrome. These take the form either of local blockades, invasive procedures involving the trigeminal nerve, and neuromodulatory procedures using superficial nerve and deep brain stimulation.

10.6.1 Local Blockades

Local blockades of pericranial nerves with anaesthetics, alcohol, phenol, or opioids, have generally been reported as ineffectual. A pterygopalatine ganglion blockade with phenol produced a variable effect in one patient (Hannerz and Linderöth, 2002), and one had a

partial response with opioid blockade of the superior cervical ganglion (Sabatowski et al., 2001). Infraorbital blockades were ineffective in eight of nine patients (Hannerz and Linderöth, 2002), and lidocaine blockades of lacrimal nerve, orbicularis oculi muscles, and the retrobulbar region also had no effect, as did a stellate ganglion block with bupivacaine (Pareja et al., 1995). In the current cohort, there was no improvement from pterygopalatine maraine injection or retrogasserian alcohol block.

Supraorbital blockades using lidocaine, bupivacaine or alcohol, have been reported as ineffective in suppressing spontaneous attacks in nine patients, but made triggering of attacks more difficult by touching the anaesthetised area (Hannerz and Linderöth, 2002; Pareja et al., 1995).

In this cohort, one SUNCT patient had a supraorbital nerve injection and one had an infraorbital nerve injection which caused numbness but the attacks were still triggerable. These would concur with the view that SUNCT and SUNA are not peripheral nerve disorders such as supraorbital neuralgia, which respond well to local nerve blockade (Sjaastad, 1999). Even though there was local numbness in the distribution of the blocked nerve, the painful attacks still occurred, which correlates to cluster headache and the persistence of painful attacks even after trigeminal nerve root section (Matharu and Goadsby, 2002a). These all support the theory that SUNCT/SUNA in particular, and the TACs in general, are generated originally from an abnormal drive in hypothalamic activity, with subsequent trigeminovascular and cranial autonomic activation.

10.6.2 Invasive surgical procedures involving the trigeminal nerve

One SUNCT patient in this series had no improvement with microvascular decompression. In the literature, two patients have been treated with the Jannetta procedure (microvascular decompression of the trigeminal nerve) with good effect at limited followup (up to 17 months) (Gardella et al., 2001; Lenaerts, 1997), although in one patient it made the symptoms worse (Matharu et al., 2004b), and in 2 further patients it was unhelpful, as were glycerol rhizotomy and γ knife radiosurgery, and in fact the

patients suffered post surgical side effects of anaesthesia dolorosa, unilateral deafness, chronic vertigo and disequilibrium (Black and Dodick, 2002). One patient underwent a right trigeminal radiofrequency thermocoagulation, after which she was pain free for 3 years, but with marked hypoanaesthesia over the second and third trigeminal distributions on that side (Matharu et al., 2004b). Therefore trigeminal surgery is generally considered only as a last resort, and then with caution, given its uncertain outcomes and the potential for side effects.

10.6.3 Hypothalamic deep brain stimulation

Functional imaging work has shown activation of the posterior hypothalamic region during attacks of cluster headache (May et al., 1998a; Sprenger et al., 2004a), and SUNCT (Cohen et al., 2004a; May et al., 1999b; Sprenger et al., 2005). Sixteen patients with intractable chronic cluster headache and one patient with intractable SUNCT have undergone deep brain electrical stimulation to the posterior hypothalamus, with good results (Leone et al., 2004a; Leone, 2004). In another series of six patients, two were painfree with a third patient with much reduced frequency of attacks. However the side effect of diplopia limited the increase of the voltage, and one patient died of an intracerebral haemorrhage (Schoenen et al., 2005). Therefore the referral of patients for these procedures is done with great caution, and currently is reserved for those patients who are refractory to all other types of treatment.

10.7 Greater occipital nerve injections

Two patients with SUNCT and six patients with paroxysmal hemicrania have undergone lidocaine blockades of the greater occipital nerve with no benefit (Antonaci et al., 1997; Pareja et al., 1995). A combination of lidocaine and a steroid in cluster headache effected a good or moderate response in nine out of 14 patients (Peres et al., 2002). This study demonstrates a moderate to good effect of greater occipital nerve injection of steroid and lidocaine in 63% of SUNCT patients. A double-blind placebo controlled study of a

mixture of long- and rapid-acting betamethasone in 16 ECH and 7 CCH patients showed a good effect in 61%, as opposed to no response with placebo (Ambrosini et al., 2005).

It may be the combination of steroid and lidocaine, or steroid alone, rather than the lidocaine itself that elicits a good response. Indeed it has been shown that suboccipital injection of local anesthetic alone have neither a beneficial nor a worsening effect on CH attacks (Anthony, 1987), and that steroid injections have been beneficial in a wide range of idiopathic headache syndromes in a group of 500 patients (Anthony, 1992). Steroids are used systemically in the treatment of cluster headache (Antonaci et al., 2005; Cianchetti et al., 1998; Couch and Ziegler, 1978; Kudrow, 1980; Mir et al., 2003). This may be linked to abnormalities in the secretion of diurnally varying hormones in CH, in particular cortisol and melatonin. Cortisol production was significantly higher and the morning cortisol peak was delayed when compared to the remission periods and healthy controls (Waldenlind et al., 1987). This may in part explain the efficacy of high-dose steroids in the treatment of CH, especially in light of the diurnal nature of occurrence of the attacks and the involvement of the hypothalamus.

However it is probably the local action of steroid on the greater occipital nerve which has the effect. It has been noticed that GON injections have a greater effect in primary headache syndromes in patients who have localized GON tenderness (Shields et al., 2004). Animal models have demonstrated an overlap of processing of nociceptive information from the C₂ level and the trigeminal nucleus caudalis (Goadsby et al., 1997), and stimulation of nociceptive afferent C-fibres of the dura mater, which is innervated by the first division of the trigeminal nerve, leads to increased excitability of second-order neurons receiving cervical input (Bartsch and Goadsby, 2003a). This mechanism might be involved in the referral of pain from trigeminal to cervical structures and might contribute to the clinical phenomena of cervical hypersensitivity in migraine and cluster headache. Suboccipital electrical stimulation has been successful in CH and hemicrania continua (Dodick et al., 2003; Schwedt et al., 2006). A series of eight patients with chronic migraine reported a beneficial effect with suboccipital stimulators, with changes on PET imaging in the dorsal rostral pons, anterior cingulate cortex and cuneus (Matharu

et al., 2004a). This suggests that suboccipital stimulators are capable of central neuromodulation, and it is possible that GON steroid injections may have a similar effect.

10.8 Other non-pharmacological procedures and alternative therapies

Acupuncture appears to have a moderate to good effect in some SUNCT patients, although the site of acupuncture, frequency and duration of treatment was not standardised. One patient tried a transcutaneous electrical nerve stimulation (TENS) machine, acupuncture, and a maxillary bite appliance, all with no effect, and has been reported previously (Matharu et al., 2004b). Acupuncture has been reported in cluster headache (Gwan, 1977), supraorbital neuralgia (Xia et al., 1987), and has been reviewed for other types of headache (Zhao et al., 2005).

10.9 SUNCT versus SUNA

It has been found in this series that the SUNA patients generally had a less favourable response to treatments than the SUNCT patients; particularly lamotrigine (68% effective in SUNCT yet only 25% in SUNA), topiramate (52% versus 0% response), and greater occipital nerve injection (63% versus 0% response).

SUNCT, with its characteristic conjunctival injection and tearing, is purported to be the syndrome which makes up the majority of this group, with cranial autonomic symptoms (Headache Classification Committee of The International Headache Society, 2004). It would be logical to assume that they share important aspects of pathophysiology; that is, an abnormality in the hypothalamus with subsequent trigeminovascular and cranial autonomic activation. There is abundant evidence that the hypothalamus has a role in mediating antinociceptive (Dafny et al., 1996; Wang et al., 1990) and autonomic responses (Lumb and Lovick, 1993), specifically trigeminovascular nociceptive pathways (Bartsch et al., 2004). A striking feature of CH, PH, SUNCT, and to a lesser extent hemicrania continua, is their cranial autonomic symptoms. It has been previously suggested that these are due to central disinhibition of the trigeminal-autonomic reflex by

the hypothalamus (Goadsby et al., 2001), possibly by direct hypothalamic-trigeminal connections (Malick et al., 2000). These hypothalamic-trigeminal connections may be instrumental in the cutaneous triggering seen in SUNCT and SUNA.

However there is differential activation of the cranial autonomic symptoms, with SUNCT having at least both conjunctival injection and lacrimation, and SUNA having at least one cranial autonomic symptom, but not both conjunctival injection and lacrimation. This may reflect a difference in the two syndromes at the level of the hypothalamic-autonomic connection, which may also have a bearing on the differential function of the hypothalamic-antinociceptive or hypothalamic-trigeminal connections. In this way it may be that SUNA is generally less responsive to the treatments which are associated with a good response in SUNCT, such as lamotrigine and topiramate.

It has been noticed that SUNCT patients had a good response by to GON injections (63%), although less so in SUNA. This may be purely due to the very small number of patients who had the GON injection (8 SUNCT, 1 SUNA), and it would therefore be premature to state that GON injections have no use in SUNA.

10.10 Summary

This study reports a case series of 52 patients (43 with SUNCT and 9 with SUNA) and their responses to various medications and treatments. SUNCT has been hitherto thought of as refractory to treatment, with isolated case reports in the literature as to the effect of pharmacological and non-pharmacological interventions. The study presents the largest case series of SUNCT/SUNA hitherto reported, and record their responses to treatments within the wider context of treatments noted previously.

In terms of diagnosis, the lack of response of SUNCT/SUNA to the blinded *Indotest* seems to be a very valuable tool in differentiating it from paroxysmal hemicrania, which by definition has an absolute response to indomethacin. Similarly the moderate to good response of all patients to intravenous lidocaine will be a strong diagnostic tool for

SUNCT/SUNA, and may also afford the patient some pain-free time after the infusion is discontinued (up to 6 months in our case series), which in these excruciatingly painful and usually suboptimally treated syndromes, is a bonus for both patient and clinician.

The good response to lamotrigine and topiramate in SUNCT, and gabapentin in SUNA, is also reported. The introduction of melatonin and pregabalin to the armoury of preventive medications is encouraging, especially in the light of melatonin's effect in cluster headache and the effect of pregabalin on sleep cycles, and the pathophysiological link to the hypothalamus. This will be further elucidated as more SUNCT/SUNA patients take these treatments.

As for non-systemic treatments, a good response to Greater Occipital Nerve injections with steroid and lidocaine is seen in SUNCT. The response is less clear in SUNA; however given the fact that the numbers treated so far are small, and the relative absence of side-effects with GON injections, it would be premature to state that GON injections have no effect in SUNA.

The absence of placebo-controlled randomised trials in SUNCT and SUNA has been discussed. Definitive answers will come from these trials, but they have proven exceptionally difficult to conduct in this group of patients, owing to the rarity of the syndromes and the reluctance of patients to take placebo treatments.

The next stage forward will be neuromodulatory procedures, in the form of occipital nerve stimulators and deep-brain hypothalamic stimulators.

In summary, SUNCT and SUNA are not as refractory to treatment as was previously thought. The recommendations as diagnostic manipulation would be lack of response to indomethacin and a good response to intravenous lidocaine. For preventive medications, lamotrigine, topiramate and gabapentin are recommended. Greater occipital nerve injections also prove useful in the treatment of these excruciatingly painful and very debilitating primary headache syndromes.

PART III. FUNCTIONAL IMAGING STUDIES IN SUNCT AND SUNA

Chapter 11

Functional MRI in attacks of SUNCT and SUNA

11.1 Introduction

SUNCT and SUNA, being TACs, are thought to share the same pathophysiology as other TACs such as CH and PH. Functional imaging with PET has demonstrated activation in the ipsilateral posterior hypothalamus in CH (May et al., 1998a; Sprenger et al., 2004a), and the contralateral posterior hypothalamic region in PH (Matharu et al., 2006b) and in hemicrania continua, which although not classified as a TAC, shares some clinical characteristics with TACs (Matharu et al., 2004c).

In PET, volume acquisition takes 90 seconds, and there is an interscan interval of at least 8 minutes in order to allow for decay of radioactivity (Matharu et al., 2004c). Therefore volumes can only be acquired once every 8 minutes at most. In contrast, fMRI has a much shorter acquisition time of 3.6 seconds per volume, and volumes can be acquired in immediate sequence. Therefore fMRI is an ideal imaging modality in short-lasting headache attacks such as in SUNCT and SUNA.

Ipsilateral posterior hypothalamic activation has been demonstrated on fMRI in SUNCT (May et al., 1999b), and bilateral activation has also been reported (Cohen et al., 2004a; Sprenger et al., 2005). Hypothalamic activation has been detected in a TAC not otherwise specified, but which was likely to be longer-lasting attacks of SUNCT (Sprenger et al., 2004b).

This study used fMRI in 12 patients with SUNCT and SUNA, to detect activation in the region of the posterior hypothalamus, either ipsilateral, contralateral to the side of attacks, or bilaterally. The *a priori* hypothesis is that there is activation in the region of the

hypothalamus, on either or both sides, during attacks of SUNCT or SUNA, as compared to the attack-free state, and that there is a differential increase in activation with increasing severity of the pain.

11.2 Methods

Twelve patients were recruited from our cohort of SUNCT and SUNA. Ten were male and two female. Two of these patients had SUNA (one male, one female), and eight patients had SUNCT. One patient (#2) had SUNCT secondary to a posterior fossa lesion, as is described in Chapter 5 and Chapter 6.14. Of the SUNCT patients, 6 had left-sided attacks during imaging. One patient (#7) could sometimes get right-sided attacks, but had none on this occasion. Three patients had exclusively right-sided attacks, and one patient had either left-or right-sided attacks equally. Of the SUNA patients, one had right-sided and one had left-sided attacks. One patient (#SUNA44) had another TAC on the right side which had been diagnosed as chronic cluster headache, and one (#34) had a history of cluster headache and migraine (Empl, 2003). The clinical characteristics are displayed in Table 11.1.

The study was approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee (REC Ref 97/033). The patients gave their written consent for the study, and were free to withdraw from the study at any time.

None of the patients who were on preventive medications were willing to come off their medications completely prior to the study, but all abstained from their medications for 24 hours prior to the scan. All were having spontaneous attacks at the time of the scan. Their medications are shown in Table 11.1.

Table 11.1

Clinical Characteristics of patients for fMRI and VBM, including concomitant diagnoses

Patient number	Diagnosis	Age	Male/ female	Left/ right attacks	fMRI	VBM	Medications and concomitant diagnoses
2	Secondary SUNCT	53	M	R	y	y	gabapentin 4800mg, lamotrigine 600mg, amitriptyline 50mg daily
SUNA44	SUNA	58	F	L	y	y	pregabalin 300mg daily
SUNA40	SUNA	35	M	R	y	y	verapamil 160mg daily <i>Also had a TAC attack (not SUNA) on the left</i>
6	SUNCT	69	F	R	y	y	gabapentin 1800mg, lamotrigine 200mg daily
7	SUNCT	52	M	L >>R	y	y	no medication
12	SUNCT	67	M	L	y	y	carbamazepine 800mg daily, temazepam 10mg daily
42	SUNCT	43	F	L	y	y	no medication
56	SUNCT	33	M	L	y	y	paracetamol and codeine combination, sertraline 50mg daily
17	SUNCT	71	M	L	y	y	gabapentin 1200mg, carbamazepine 400mg daily
23	SUNCT	39	M	R or L	y	y	no medication
33	SUNCT	67	M	R	y	y	no medication
34	SUNCT	62	M	L	y	y	gabapentin 1200mg, tramadol as required <i>Also had cluster headache and a history of migraine</i>
13	SUNCT	58	M	R	n	y	carbamazepine 800mg, lamotrigine 600mg daily
15	SUNCT	65	M	L	n	y	gabapentin 900mg, indomethacin 75mg daily

11.3 Image Acquisition

MRI scanning was performed on a 1.5 Tesla magnetic resonance imaging (MRI) system (Siemens Vision). A high resolution (1 x 1 x 1 mm voxel size) T1- weighted structural MRI was acquired for each subject. In each functional imaging session a total of 170 MRI volumes (40 axial slices per scan, slice thickness 2 mm) were acquired using a gradient echo echo-planar (EPI) T2* sensitive sequence (TR 3600 ms, slice time 90 ms). The images were oriented at an angle of -25° to the horizontal. The same scanner parameters and scanner hardware were used for the acquisition of all anatomical volumes.

The subject's head was positioned in a standard head coil with foam pads and earphones to protect the subject's ears from the noise of the scanner. Each patient kept their eyes open. The first four volumes were discarded to allow for T1 equilibration effects.

11.4 Headache Protocol

Once every 3.96 seconds during the scanning session, the patients received a pure 250Hz tone auditory stimulus via the headphones. On hearing this tone they were asked to rate the severity of their pain at that time. Ratings were delivered via a keypad with 4 buttons, corresponding to index finger = zero (no attack); middle finger = 1, ring finger = 2 and little finger = 3; which corresponded to attack present at mild, moderate or severe intensity respectively. The patients practised the keypresses with the auditory stimulus prior to being placed in the scanner. All patients had spontaneous attacks whilst in the scanner except Patient #17, for whom some attacks were triggered by touching the ipsilateral eyebrow. These attacks lasted well beyond the duration of the trigger stimulus and were captured during imaging.

A PC running customized software (COGENT) was used to present the auditory stimuli and record the patients' ratings. It recorded the time of auditory stimuli and time of finger presses. The onset of each patient's headache 'event' was calculated as starting at the

time of the previous auditory stimulus. The same PC and COGENT script were used for all patients.

Each scan lasted 10 minutes, with 150 tones and responses in each session. Patients underwent between 1-5 functional scans, depending on the individual patient.

One patient (#SUNA44) had an attack of his TAC on the right side in the fifth scanning session, but the first 4 sessions were purely SUNA attacks.

11.5 Analysis of Images

Data were analysed on a Dell PC using Matlab 6.5 (The MathWorks Inc., Natick, MA, USA) and statistical parametric mapping SPM2 (www.fil.ion.ucl.ac.uk/spm/spm2.html). The software analysis package was used to pre-process the functional images as follows:

- 1) realignment to correct the functional images for temporally asynchronous slice acquisition and head movement
- 2) normalisation to warp the functional images to standard space (Talairach and Tournoux, 1988)
- 3) spatial smoothing with a Gaussian filter of 4 mm FWHM (full width half maximum) in the x -, y - and z -planes (Friston et al., 1995a; Friston et al., 1995b).

Data analysis was performed using the general linear model (GLM) and modelled the different trials (headache, sound, press) as delta functions convolved with a canonical haemodynamic response as implemented in SPM2. The design matrix was modelled as an event-related experiment. The headache event was modelled in the design matrix as lasting 3.96 seconds and the 'sound' and 'press' events were modelled as lasting 0 seconds, in order to conform better to the haemodynamic response function.

The headache was assessed parametrically with rating, both in a binary sense (0 = no headache, 1 = attack of any intensity), and in a linear parametric model with a polynomial

order of 1 (0 = no headache; and 1, 2, 3 = attack of mild, moderate or severe intensity respectively).

Each patient's dataset was assessed independently. Patients underwent between 1-5 sessions, and in cases of more than 1 session, these were analysed in a fixed-effects single design matrix. An example of the design matrix for one patient who underwent one session is shown in Figure 11.1, and for one patient who underwent four sessions in Figure 11.2.

Voxel-wise regression coefficients for all regressors were estimated using weighted least squares (WLS) within SPM2. Effects were tested with appropriate linear contrasts of the regression coefficients, resulting in a t statistic for each voxel. The T test was performed for both directions of effects, *e.g.* an activation or a deactivation (Josephs and Henson, 1999). An example of a contrast for positive activation is shown in Figure 11.1, and for negative activation is shown in Figure 11.2.

11.6 Testing for effects at the hypothalamus

When making inferences about regional effects (*e.g.* activations) in SPMs, one often has some idea about where the activation should be. In this instance a correction for the entire search volume is inappropriate. However, a problem remains in the sense that one would like to consider activations that are 'near' the predicted location, even if they are not exactly coincident. There are two approaches one can adopt; (i) pre-specify a small search volume and make the appropriate Gaussian Random Field (GRF) correction (Worsley, 1996) or (ii) used the uncorrected p value based on spatial extent of the nearest cluster (Friston, 1997), according to the size of the structure of interest. This probability is based on getting the observed number of voxels, or more, in a given cluster (conditional on that cluster existing).

Design matrices for individual patient analysis

Figure 11.1

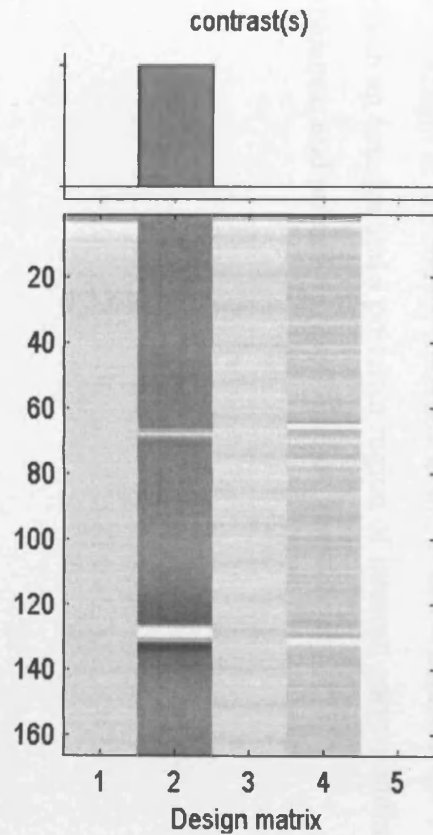


Figure 11.2

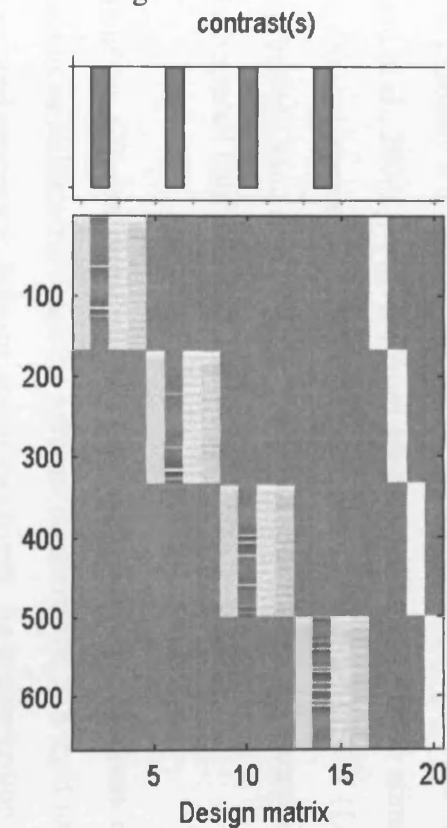


Figure 11.1. The design matrix for one scanning session in one patient. Each horizontal line (numbered up to 166) represents an image volume acquisition in time. For each image, Column 1 represents the headache, Column 2 represents the headache as parametrically assessed with rating (0, 1, 2, 3). Column 3 represents the auditory stimulus, and Column 4 represents the finger press. Column 5 is the error, after the General Linear Model (Friston et al., 1995b). The contrast vector is $[0 \ 1 \ 0 \ 0 \ 0]$, that is a T test for positive activation for headache as parametrically assessed with rating.

Figure 11.2. The design matrix for a patient undergoing 4 scan sessions. The contrast vector is $[0 \ -1 \ 0 \ 0 \ 0 \ -1 \ 0 \ 0 \ 0 \ -1 \ 0 \ 0 \ 0 \ 1 \ -0 \ 0 \ 0 \ 0 \ 0 \ 0]$, i.e. a T test for negative activation for headache as parametrically assessed with rating.

11.7 Locating the hypothalamus

The coordinates for the region of interest, being the hypothalamus, were determined from reports in published studies of hypothalamic activation on functional imaging in CH (May et al., 1998a; May et al., 2000; Sprenger et al., 2004a), PH (Matharu et al., 2006b), SUNCT (Cohen et al., 2004a; Sprenger et al., 2005), a TAC not otherwise specified but which is probably a longer-lasting attack of SUNCT (Sprenger et al., 2004b) and HC (Matharu et al., 2004c), and also from coordinates for deep brain stimulation in CH (Leone, 2001; Leone et al., 2004a; Schoenen et al., 2005), SUNCT (Leone et al., 2005) and aggression (Sano et al., 1970). These were normalized to a standard stereotactic Talairach space (Talairach and Tournoux, 1988).

A table of the different coordinates is presented (Table 11.2), where x , y and z are the coordinates as millimetres from the anterior commissure, in a right to left, anterior to posterior, and superior to inferior axis respectively. As is convention, positive values for x , y and z indicate right, anterior and superior respectively. T tests were applied both for positive and negative activation, as shown in Figures 11.1 and 11.2. Each region of interest was specified as a 10mm sphere with these coordinates at the centre.

It can be seen that these results are not consistent between studies, and some studies have reported at more anterior sites, especially in SUNCT and the atypical TAC (Cohen et al., 2004a; Sprenger et al., 2004b; Sprenger et al., 2005). Therefore the T test was applied using both an anterior and a posterior region of interest, corresponding to the area of the hypothalamus and posterior hypothalamus, respectively.

Table 11.2 Coordinates for hypothalamic functional imaging and deep brain stimulation in previous studies

Functional imaging	Diagnosis	x	y	z
May et al Lancet 1998	CH	-2	-18	-8
May et al Neurology 2000	CH	-2	-18	-8
Sprenger et al Neurology 2004	CH	-4	-14	-6
Matharu et al Ann Neurol 2006	PH	+/-6	-16	-6
May et al Ann Neurol 1999	SUNCT	Not specified		
Sprenger et al Cephalalgia 2004	Atypical TAC	6	-8	0
Cohen et al Cephalalgia 2004	SUNCT	+/-4	-6	-2
Sprenger et al Pain 2005	SUNCT	-6	-6	-6
Matharu et al Headache 2004	HC	6	-14	-6
Stimulation	Diagnosis	x	y	z
Franzini et al Neuromodulation 2004	CH stimulation	+/-2	-15	-8
Leone et al Brain 2004	CH stimulation	+/-2	-18	-8
Schoenen et al Brain 2005	CH stimulation	+/-2	-18	-8
Leone et al NEJM 1991	CH stimulation	2	-18	-8
Leone et al Ann Neurol 2005	SUNCT stimulation	2	-15	-5
Sano et al 1970 J Neurosurg- stimulation for aggression No T&T coordinates given: 'from 1mm anterior to the midpoint of the intercommissural line to 2mm posterior to the midpoint (most often the midpoint itself), 2-4mm below the intercommissural line, 2mm lateral to the lateral wall of the 3 rd ventricle' Probably +/-6, -11/-14, -2/-4				

11.8 Group Analysis

In order to assess the effects across the group of SUNCT patients, group analyses were performed. These included only patients with primary (idiopathic) SUNCT, and thus excluded the two patients with SUNA and one patient with symptomatic SUNCT.

Two group analyses were performed; a fixed-effects and a random (mixed) effects analysis.

Fixed-Effects analysis

The fixed-effects analysis was a first-level analysis, in which all patients' scans were included in one large design matrix (Figure 11.3), and this assessed mainly intra-patient variability.

The patients' normalised images were smoothed to a Gaussian smoothing kernel of 8mm FWHM. Intersubject statistical analysis requires a large enough smoothing kernel filter to compensate for the large interindividual variability.

Two patients with right sided attacks (#6 and #33) had their images flipped so that all patients' attacks were assessed as coming from the same (left) side. The normalised images were flipped from right to left using SPM2, with the formula

$$(i1 + flipud(i1))/2$$

in Image Calculation (ImCalc), and these flipped images were subsequently smoothed to 8mm FWHM.

The contrast was performed by a *T*-test at 'headache parametrically associated with pain rating' at each session for each patient. *T*-tests were performed in two analyses, one to assess positive activation, and one to assess negative activation. *T* tests were applied to regions of interest as spheres of 10mm diameter at the anterior and posterior coordinates of the hypothalamus at both sides, as for individual patients.

Random-Effects analysis

The random (mixed) effects analysis was a basic model second-level analysis, in which the contrasts from each patient's individual analysis were taken to the second level and assessed as part of a group (Worsley et al., 2002). This analysis assesses mainly inter-patient variability, and the inferences can be generalised to the population from which the patients were drawn.

For each patient, four contrasts (*con* images) were taken, corresponding to the following states:

- 1) headache parametrically varying to pain rating (positive)
- 2) headache parametrically varying to pain rating (negative)
- 3) headache with binary variation (attack on/off) (positive)
- 4) headache with binary variation (attack on/off) (negative) activations

Each of these 4 *con* images per patient was smoothed to 8mm FWHM using SPM2. For the two patients with right-sided attacks, their *con* images were flipped in SPM2 using the formula

flipud (i1)

in Image Calculation (ImCalc), and then smoothed to 8mm FWHM.

A single design matrix was constructed at the second-level for each of the four contrasts: headache according to pain rating headache according to pain rating (negative), and headache with binary variation (positive), and headache with binary variation (negative). An example is shown in Figure 11.4.

A *T*-test was applied for each design matrix as shown in Figure 11.4. *T*-tests were applied to regions of interest as spheres of 10mm diameter at the anterior and posterior coordinates of the hypothalamus at both sides, as for individual patients.

Design matrices for group analysis
Figure 11.3

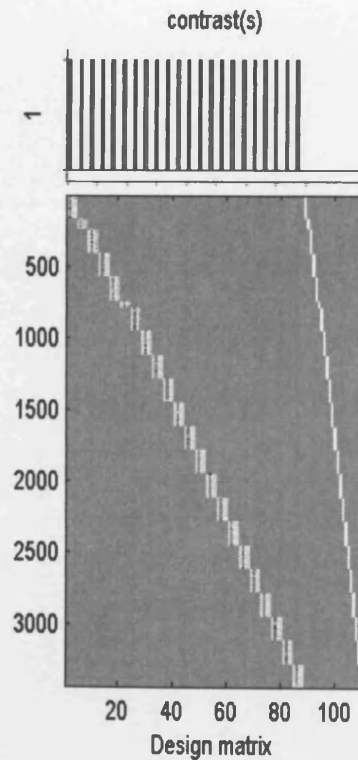


Figure 11.3 Fixed-effects group analysis for 9 patients. Each session for each patient is represented within the matrix (22 sessions in total), and the contrast set is (0 1 0 0) repeated 22 times, with 22 zeros for the error estimate.

Figure 11.4

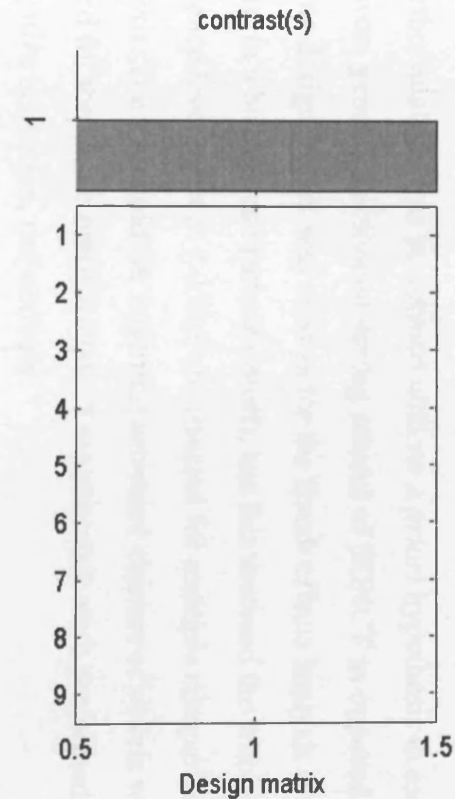


Figure 11.4 Random-effects group analysis for 9 patients. Each patient's contrast (for example headache parametrically assessed with rating) was taken to a second-level design matrix; therefore there is only one contrast and no error estimates in this model.

11.9 Group Analysis with no *a priori* hypothesis

All of the previous analyses were performed on the basis of the *a priori* hypothesis that there was activation in the area of the hypothalamus during attacks of SUNCT/SUNA. One further analysis was performed with no *a priori* hypothesis to ascertain the structures which were generally activated during attacks of SUNCT as opposed to the painfree state. The same design matrix was used as for the fixed- effects analysis (Figure 11.3) for headache in a binary state (attack on/off), but this assessed the whole brain SPM with significance level set at $P \leq 0.001$ uncorrected for multiple comparisons, with no *a priori* hypothesis. The threshold for reporting activated clusters of voxels was set at $P < 0.05$ corrected for the whole brain volume. Two contrasts were performed, one for positive and negative activation, respectively.

Chapter 12

Results- Functional MRI in attacks of SUNCT and SUNA

12.1 Psychophysical Data

Patient #2- Symptomatic SUNCT- right sided attacks

The patient underwent 5 scanning sessions. The first one was stopped after 22 volumes (79.2 seconds) as the patient had defaulted on some keypresses. This scan was still used in the final analysis, as the patient reported that the default non-keypresses corresponded to the painfree state. He had spontaneous attacks as follows:

Session 1: 4 attacks (mild to severe)

Session 2: 9 attacks (mild)

Session 3: 24 attacks (mild)

Session 4: 12 attacks (mild)

Session 5: 22 attacks (mild to moderate)

Attacks lasted between 3.96 seconds (the time between consecutive auditory tones) and 305 seconds.

Patient #SUNA44- SUNA- left sided attacks

The patient underwent 3 scanning sessions. She only had attacks in the second session, where she had 2 mild spontaneous attacks, of 3.96 and 15.8 seconds' duration each. Scanning was terminated after the third session at the patient's request.

Patient #SUNA40- SUNA-right sided attacks, and a TAC on the left side

The patient had right-sided SUNA attacks, but also had a separate TAC on the left side, with left periorbital and nasal pain with ipsilateral conjunctival injection, nasal congestion, and a feeling of ear fullness. There was ipsilateral photophobia and phonophobia, and agitation. Each attack lasted an hour. He had 2-3 attacks a week, sometimes triggered by alcohol. He originally had bouts of a few weeks with remissions of 6-8 weeks, although the remissions had reduced in length. This had been diagnosed as

secondary chronic cluster headache. As an abortive he would have sumatriptan 6mg subcutaneously, and was taking verapamil 160 mg daily as a preventive, which would suppress the pain but he would still have occasional attacks, comprising predominantly autonomic symptoms. He could easily distinguish between the two types of attacks.

He underwent 5 scanning sessions. He had spontaneous attacks as follows:

Session 1: 9 mild SUNA attacks

Session 2: 10 SUNA attacks (mild to moderate)

Session 3: 4 SUNA attacks (moderate)

Session 4: 11 SUNA attacks (mild to moderate)

Session 5: spontaneous TAC; although this manifested itself as 19 episodes of mild to moderate pain separated by some painfree episodes.

SUNA attacks lasted 3.96-35.6 seconds each. The TAC episodes lasted 3.96-91.1 seconds.

For the purposes of this study, the contrast vector only applied to the SUNA sessions.

Patient #6- SUNCT- right sided attacks

The patient underwent 3 sessions. The second session was stopped after 76 volumes (273 sec) because the stimulus PC crashed. The data was recovered for use in the analysis. She had spontaneous attacks as follows:

Session 1: 10 attacks (mild to severe)

Session 2: 1 attack (ranged from mild to severe)

Session 3: 4 attacks (mild to moderate)

Attacks lasted between 3.96-455 seconds.

Patient #7- SUNCT- left sided attacks

This patient had left sided attacks during the scanning sessions. He can also have right-sided attacks, but had none on this occasion. He underwent 4 sessions but had pain only in the first session. This was a spontaneous attack lasting 23.8 seconds (ranged from mild to moderate). Only this session was included in the analysis.

Patient #12- SUNCT- left sided attacks

The patient underwent 5 scanning sessions. In the first and second sessions he had no attacks. He had spontaneous attacks as follows:

Session 3: 6 mild attacks

Session 4: 7 mild attacks. This session was stopped early as the patient then tried to trigger an attack whilst in the scanner. The first 50 scans' worth of data (200 sec) was included in the analysis.

Session 5: 12 attacks

Attacks lasted between 3.96 and 7.92 seconds each. Only these sessions were included in the analysis.

Patient #42- SUNCT- left sided attacks

The patient underwent one scanning session. She had 5 mild attacks, lasting 19.8- 103 seconds each.

Patient #56- SUNCT-left sided attacks

The patient underwent 4 scanning sessions. He had spontaneous attacks as follows:

Session 1: 4 mild attacks

Session 2: 4 mild attacks

Session 3: 6 mild attacks

Session 4: 13 mild attacks

Attacks lasted between 3.96 and 15.8 seconds each.

Patient #17- SUNCT- left sided attacks

The patient underwent 4 scanning sessions. There were no attacks in the first session, so this was excluded from the analysis. The remaining sessions were started after an attack was triggered by touching the ipsilateral side of the face. The attacks lasted long after the stimulus was removed, and were therefore captured in the scanner.

Session 1: 1 attack (mild-moderate)

Session 2: 1 attack (mild-moderate)

Session 3: 1 attack (mild-severe)

Attacks lasted 95-115 seconds each.

Patient #23- SUNCT- attacks on both sides

The patient underwent 4 scanning sessions. He had spontaneous attacks in the first three sessions, and these were included in the analysis. Spontaneous attacks occurred on either right or left side at random. There was no way of recording the laterality of the attacks in the scanner.

Session 1: 4 attacks (mild-moderate)

Session 2: 3 mild attacks

Session 3: 2 mild attacks

Attacks lasted 3.96-162 seconds each.

Patient #33- SUNCT- right sided attacks

The patient underwent 3 scanning sessions. He only had 2 spontaneous attacks, both in the third session, lasting 3.96 and 7.92 seconds, and being mild and moderate in severity respectively. This session was used for analysis.

Patient #34- SUNCT- left sided attacks, left sided cluster headache, and migraine

This patient had migraine, CH and SUNCT and has been the subject of a previous case report (Empl et al., 2003). He underwent 3 scanning sessions, during which he had a dull background ache on the left side which was attributable to his CH. He had spontaneous SUNCT attacks, all of which were distinguishable from the CH, as follows:

Session 1: 18 attacks (mild-moderate)

Session 2: 14 attacks (mild-moderate)

Session 3: 11 attacks (mild-severe)

Attacks lasted between 3.96 and 107 seconds.

12.2 Individual Patient Results

Results were analysed on uncorrected whole brain statistical parametric maps with a threshold of $P < 0.01$. Activated voxels were reported at $P \leq 0.001$ uncorrected, within a sphere of 10mm radius corresponding to the region of interest, with centre as the coordinates of either anterior or posterior hypothalamus, on right or left side.

The results, including Z scores at each activated voxel, are shown in Table 12.1. In all figures the coloured bar represents the Z score, with different coloured clusters of voxels corresponding to different Z scores.

Patient #2- Symptomatic SUNCT- right sided attacks

There were no significant activations in the anterior or posterior regions on either side. There was positive activation in the region of the right posterior hypothalamus, both on parametric and binary analysis (T test at 6, -16, -6), but this did not survive the significance at $P \leq 0.001$.

Patient #SUNA44- SUNA- left sided attacks

There was no significant positive activation. There was significant negative activation in the posterior region bilaterally on binary analysis (as the patient only had mild attacks). A T -test at (6, -16, -6) showed an activated voxel at (2, -14, -14) (**Figure 12.1**) and a T -test at (-6, -16, -6) showed an activated voxel at (0, -14, -14).

Table 12.1 Activations for individual patients in the region of interest (anterior or posterior hypothalamic area)

Patient	Diagnosis	Side	Activations		coordinates tested			coordinates where $P \leq 0.001$			Z score ($P \leq 0.001$)
			location	polarity of activation	x	y	z	x	y	z	
#SUNA44	SUNA	L	right posterior	negative	6	-16	-6	2	-14	-14	3.02
			left posterior	negative	-6	-16	-6	0	-14	-14	2.99
#SUNA40	SUNA	R	right posterior	negative	6	-16	-6	6	-16	2	3.2
			right anterior	negative	6	-8	0	6	0	-6	3.85
			left anterior	negative	-6	-8	0	6	-16	2	3.12
#6	SUNCT	R	right posterior	negative	6	-16	-6	10	-6	-4	3.12
			right anterior	negative	6	-6	-6	8	-2	-10	3.89
#7	SUNCT	L (bilateral)	right posterior	positive	6	-16	-6	0	-18	-12	4.39
			left posterior	positive	-6	-16	-6	0	-18	-12	4.39
#12	SUNCT	L	right posterior	positive	2	-18	-8	0	-14	0	3.17
			left posterior	positive	-6	-16	-6	-4	-6	-4	3.09
			left anterior	positive	-6	-6	-6	-4	-6	-4	3.09
#42	SUNCT	L	right posterior	positive	6	-16	-6	8	-14	-6	3.17
			right anterior	negative	6	-8	0	0	-2	-2	4.08
			left anterior	negative	-6	-8	0	-2	-2	-2	4.26
#56	SUNCT	L	right posterior	positive	6	-16	-6	8	-20	-12	3.09
#17	SUNCT	L	right posterior	positive	6	-16	-6	8	-10	-14	4.85
			left posterior	positive	-2	-18	-8	-6	-16	-6	3.8
			left anterior	positive	-6	-8	0	-4	-6	-2	3.95
			right anterior	positive	6	-8	0	2	-6	-2	3.59

Table 12.1 ctd

patient	diagnosis	side	activations								
			location	polarity of activation	coordinates tested			coordinates where $P \leq 0.001$			Z score ($P \leq 0.001$)
					x	y	z	x	y	z	
#23	SUNCT	bilateral	right posterior	positive	6	-16	-6	4	-12	-14	4.1
			right anterior	positive	6	-6	-6	6	-8	-10	3.26
					6	-8	0	8	-6	0	2.99
			left posterior	positive	-6	-16	-6	-12	-16	-10	3.31
			left anterior	positive	-6	-8	0	-2	-2	6	3.41
#33	SUNCT	R	right posterior	negative	6	-16	-6	16	-14	-6	3.07
					6	-16	-6	6	-4	-6	3.38
			right anterior	negative	6	-6	-6	6	-4	-8	2.97
					6	-6	-6	6	-2	-4	3.13
#34	SUNCT	L	right posterior	positive	6	-16	-6	2	-14	-14	3.95
					6	-16	-6	2	-16	-16	5.2
			right anterior	positive	6	-6	-6	6	-2	-12	4.87
			left anterior	positive	-6	-6	-6	-2	-10	-14	3.47
			left posterior	positive	-6	-16	-6	-2	-10	-14	3.47

Figure 12.1
Negative activation in Patient #SUNA44

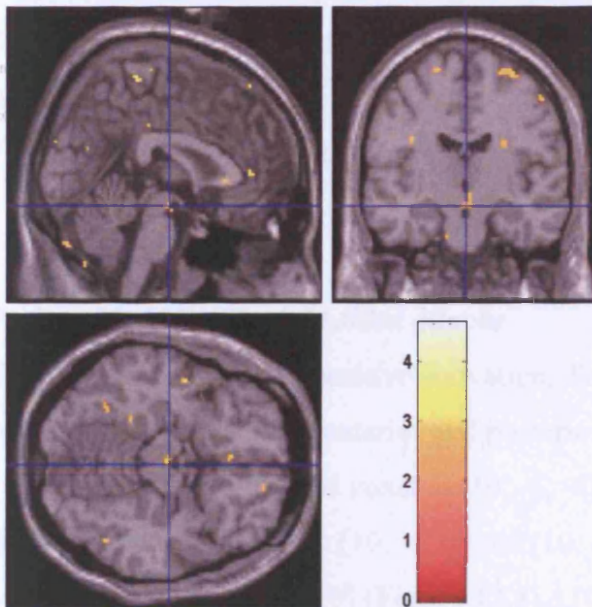


Figure 12.1
Negative activation at (2, -14, -12)

Figure 12.2
Negative activation in Patient #SUNA40

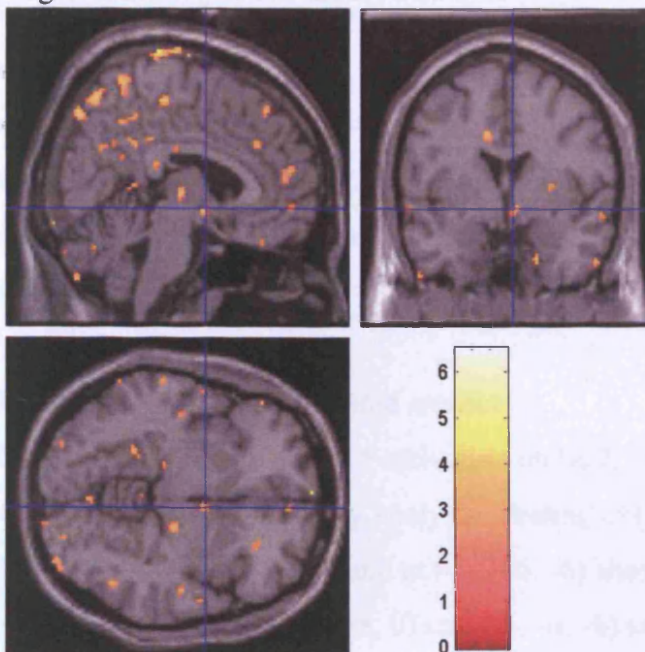


Figure 12.2
Negative activation at (6, 0, -6)

Patient #SUNA40- SUNA-right sided attacks, and a TAC on the left side

There was negative activation in both the anterior and posterior regions on the right side, and in the anterior region on the left side, when the analysis was set for SUNCT attacks only. For parametric analysis, testing at (6, -16, -6) showed an activated voxel at (6, -16, 2) and testing at (6,-8, 0) showed an activated voxel at (6, 0, -6). For binary analysis, testing at (6,-8, 0) showed an activated voxel at (6, 0, -6). This is shown in **Figure 12.2**. Testing at (-6, -8, 0) showed an activated voxel at (6, -16, 2).

Patient #6- SUNCT- right sided attacks

There was no significant positive activation. There was significant negative activation on parametric analysis in the anterior and posterior regions on the right side. Testing at (6, -16, -6) showed an activated voxel at (10, -6, -4) (**Figure 12.3**), and testing at (6, -8, 0) showed activated voxels at (10, -4, 0) and (10, -4, -8). Testing at (6, -6, -6) showed activated voxels at (8,-2,-10) (**Figure 12.4**), (10,-4, 0) and (12,-6,-4).

Patient #7- SUNCT- left sided attacks

There was significant positive activation in the posterior region when *T*-tests were applied to left or right sides. On parametric analysis, testing at (2, -18, -8) showed an activated voxel at (0, -18, -14). Testing at (6, -16, -6) and at (-6, -16, -6) showed an activated voxel at (0, -18, -12) (**Figure 12.5**). On binary analysis, testing at (2, -18, -8) showed an activated voxel at (0, -18, -14) and testing at (-6, -16, -6) showed an activated voxel at (0, -18, -12).

Patient #12- SUNCT- left sided attacks

There was significant positive activation on both sides in the posterior region, and in the left anterior region, on binary analysis. Testing at (2, -18, -8) showed an activated voxel at (0, -14, 0) (**Figure 12.6**), and at (-6, -16, -6) showed activated voxels at (-4, -6, -4) and (-12, -18, 0). Testing at (-6, -8, 0) and (-6, -6, -6) showed activated voxels at (-4, -6, -4) (**Figure 12.7**) and (-12, -18, 0).

Figures 12.3 and 12.4
Negative activation in Patient #6

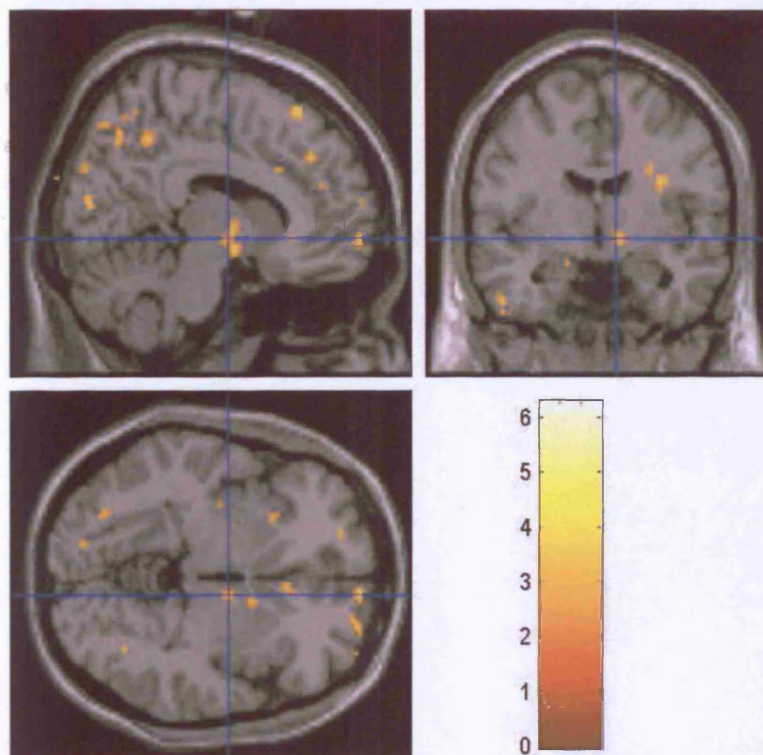


Figure 12.3
Negative activation at (10, -6, -4)

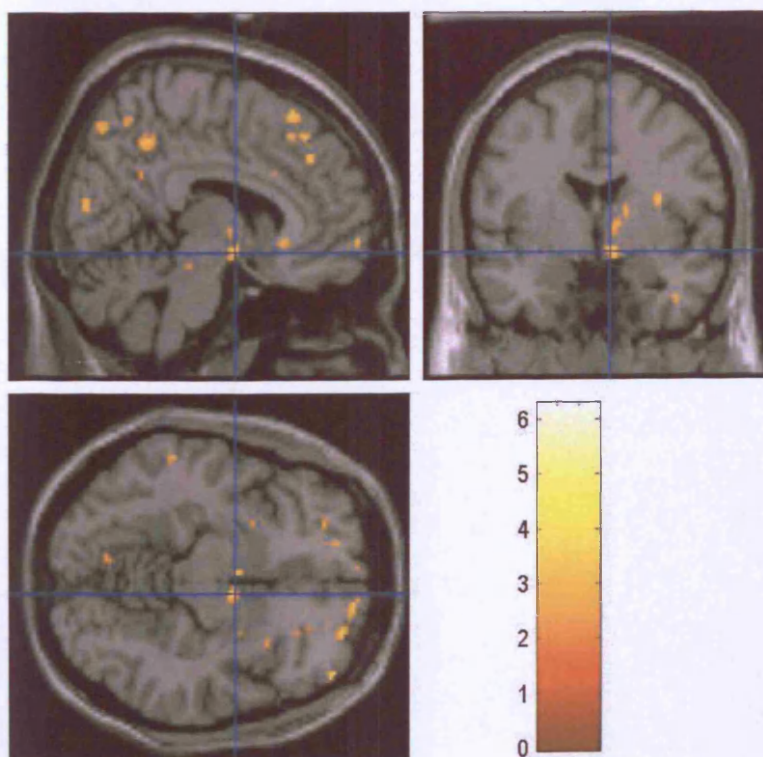


Figure 12.4
Negative activation at (8, -2, -10)

Figure 12.5
Positive activation in Patient #7

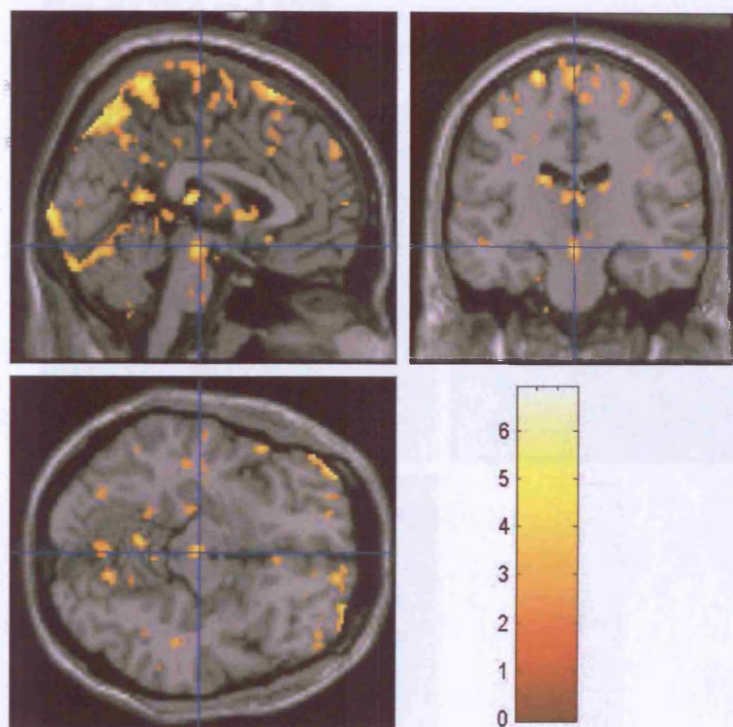


Figure 12.5
Positive activation at (0, -18, -12)

Figure 12.7
Positive activation at (-4, -6, -4)

Figures 12.6 and 12.7
Positive activation in Patient #12

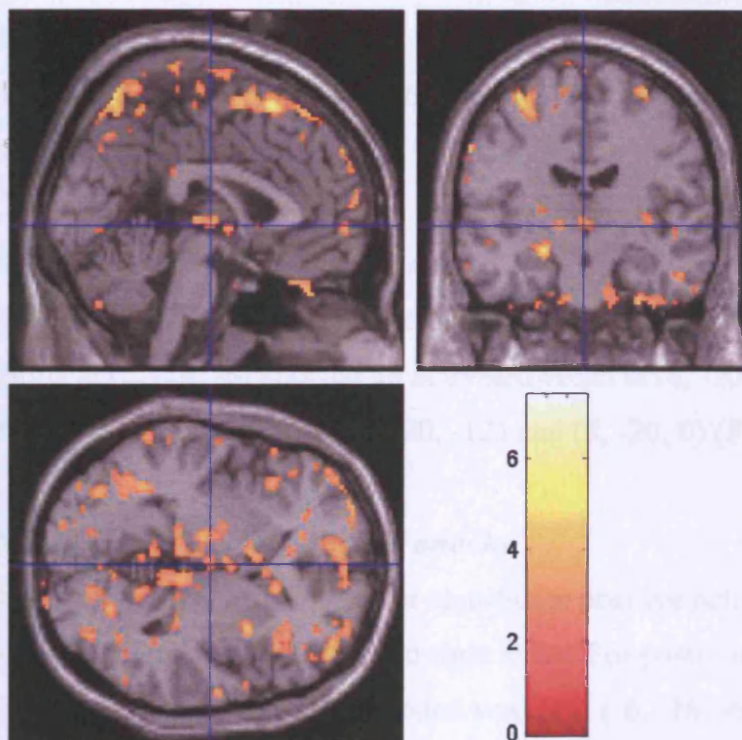


Figure 12.6
Positive activation at (0, -14, 0)

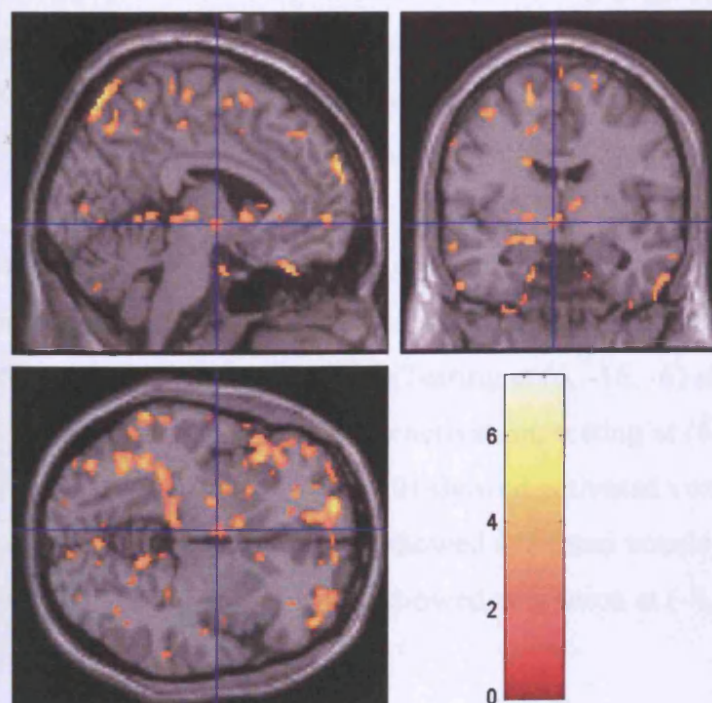


Figure 12.7
Positive activation at (-4, -6, -4)

Patient #42- SUNCT- left sided attacks

There was significant positive activation in the right posterior region. Testing at (2, -18, -8) and (6, -16, -6) showed an activated voxel at (8, -14, -6) (**Figure 12.8**). There was significant negative activation in the anterior region on both sides. Testing at (6, -8, 0) showed an activated voxel at (0, -2, -2), and testing at (-6, -8, 0) showed an activated voxel at (-2, -2, -2). Testing at (6, -6, -6) and (-6, -6, -6) both showed an activated voxel at (-2, -2, -2) (**Figure 12.9**).

Patient #56- SUNCT-left sided attacks

There was significant positive activation in the right posterior region. On binary analysis, testing at (2, -18, -8) showed an activated voxel at (8, -20, -14); and testing at (6, -16, -6) showed activated voxels at (8, -20, -12) and (8, -20, 0) (**Figure 12.10**).

Patient #17- SUNCT- left sided attacks

On parametric analysis there was significant positive activation in both anterior and posterior regions on both left and right sides. For posterior activation, testing at (2, -18, -8) and (-2, -18, -8) showed activated voxels at (-6, -16, -6) (**Figure 12.11**). Testing at (6, -16, -6) showed activated voxels at (8, -10, -14) (**Figure 12.12**). For anterior activation, testing at (6, -8, 0) showed an activated voxel at (2, -6, -2) (**Figure 12.13**). Testing at (-6, -8, 0) showed activated voxels at (-6, -16, -6) and (-4, -6, -2) (**Figure 12.14**). Testing at (6, -6, -6) showed activated voxels at (6, -4, -12), (-2, -6, -2) and (8, -10, -14).

On binary analysis there was significant positive activation in both anterior and posterior regions on both left and right sides. For posterior activation, testing at (2, -18, -8) showed activated voxels at (6, -20, -14) Testing at (6, -16, -6) showed activated voxels at (8, -12, -14) and (2, -6, -2). For anterior activation, testing at (6, -8, 0) showed an activated voxel at (2, -6, -4). Testing at (-6, -8, 0) showed activated voxels at (-4, -6, -4), (2, -6, -4) and (-4, -2, -6). Testing at (6, -6, -6) showed activated voxels at (2, -6, -4), (-2, -2, -2) and (8, -10, -12). Testing at (-6, -6, -6) showed activation at (-4, -2, -6), (2, -6, -4) and (-4, -6, -4).

Figures 12.8 and 12.9

Positive and Negative activation in Patient #42

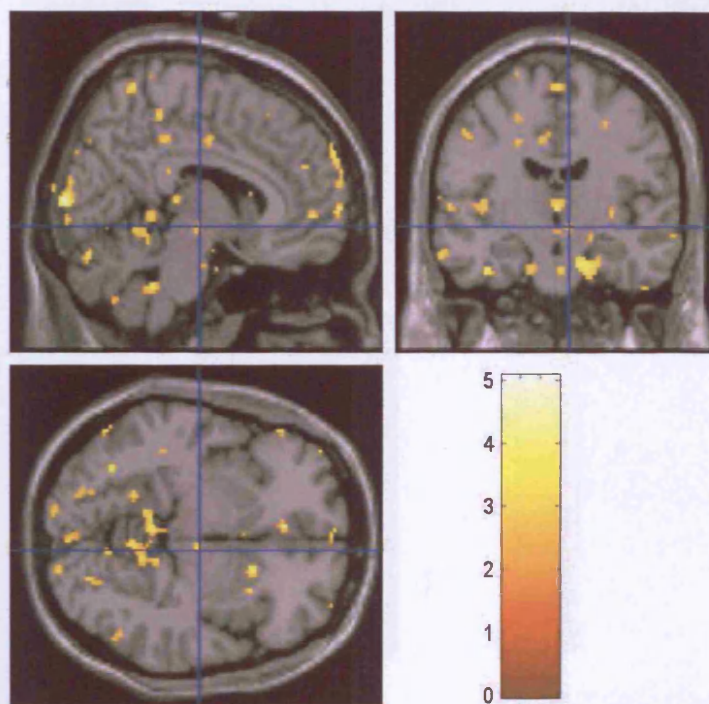


Figure 12.8

Positive activation at (8, -14, -6)

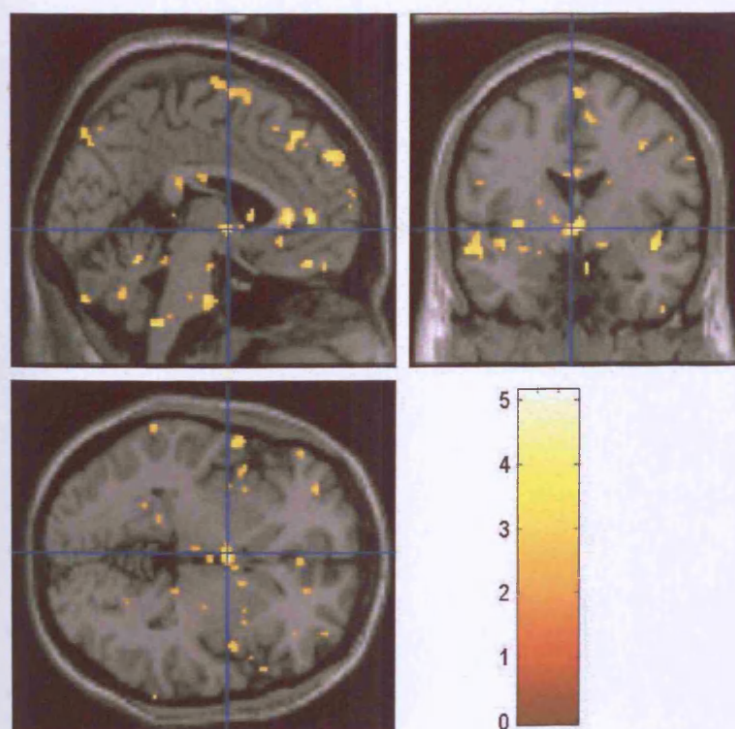


Figure 12.9

Negative activation at (-2, -2, -2)

Figure 12.10
Positive activation in Patient #56

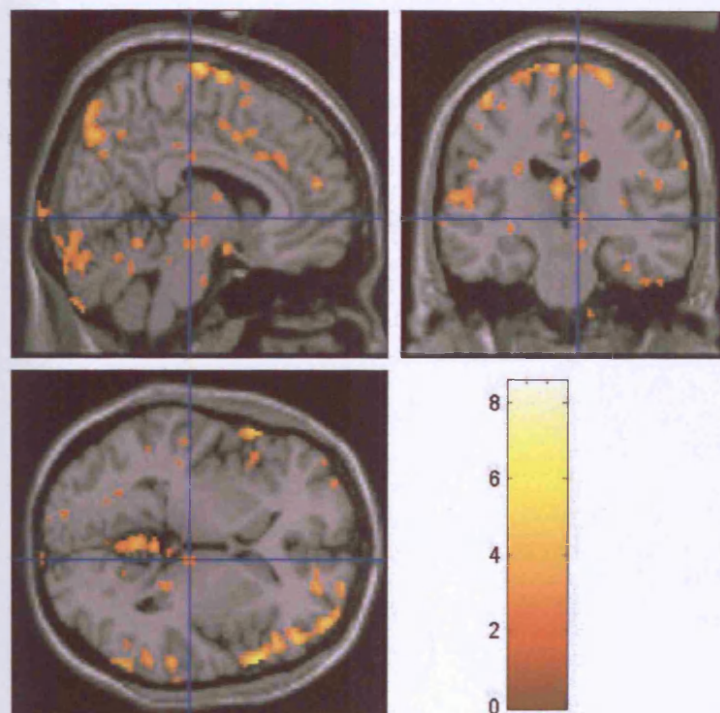


Figure 12.10
Positive activation at (8, -20, 0)

Figures 12.11 and 12.12

Positive activation bilaterally in posterior regions in Patient #17

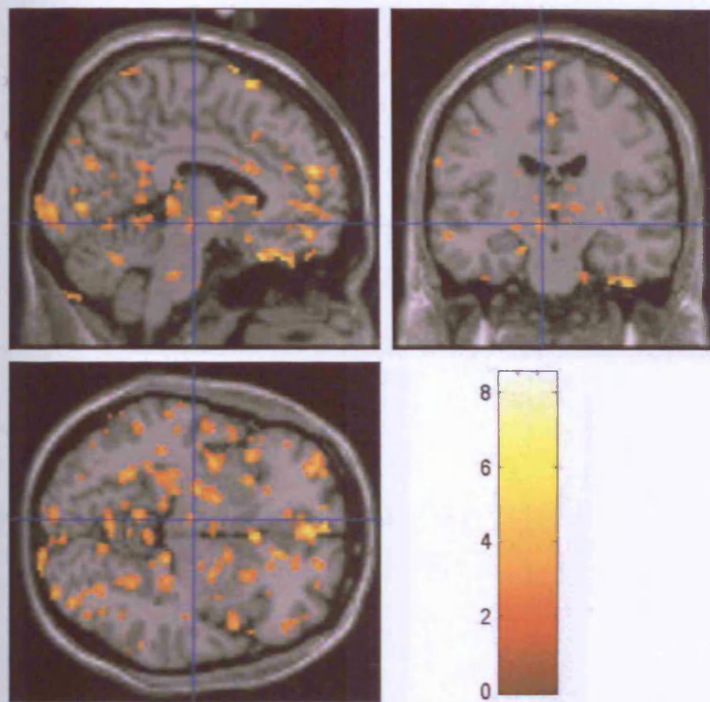


Figure 12.11
Positive activation at (-6, -16, -6)

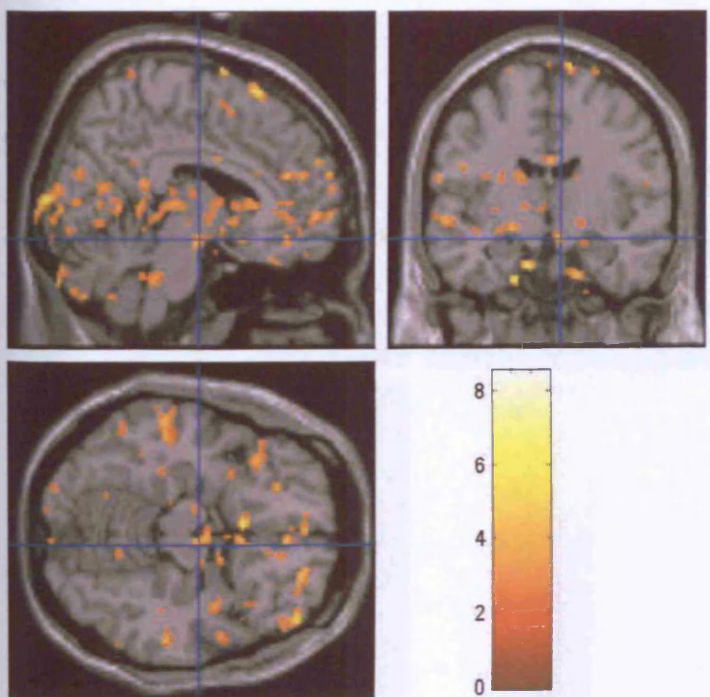


Figure 12.12
Positive activation at (8, -10, -14)

Figures 12.13 and 12.14

Positive activation bilaterally in anterior regions in Patient #17

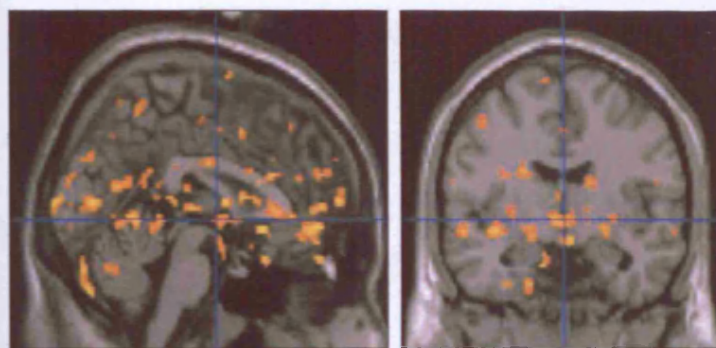


Figure 12.13

Positive activation at (2, -6, -2)

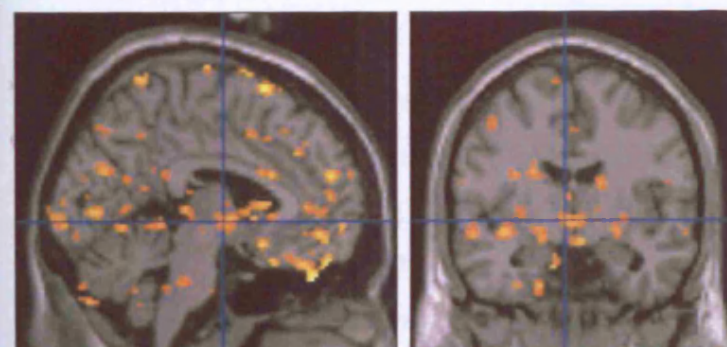
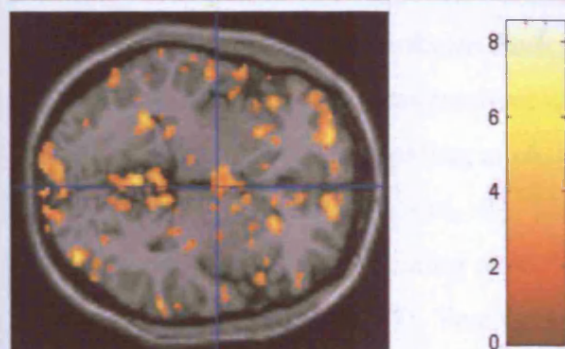
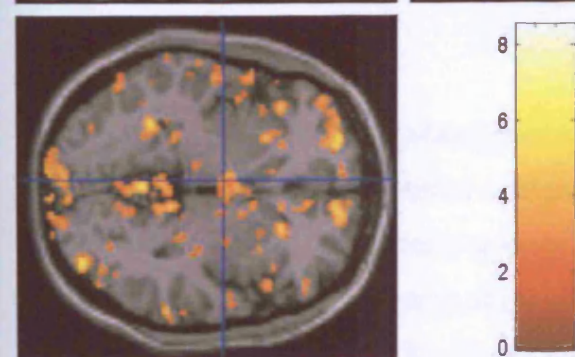


Figure 12.14

Positive activation at (-4, -6, -2)



There was also negative activation on parametric analysis. Testing at (2, -18, -8) showed activation at (10, -12, -8), (-6, -12, -8) and (-4, -18, -16). Testing at (-2, -18, -8) showed activation at (-6, -12, -8) and (-4, -18, -16). Testing at (6, -8, 0) showed activation at (10, -12, -8). Testing at (-6, -8, 0) showed activation at (-6, -12, -8). Testing at (-6, -14, -6) showed activation at (-6, -12, -8), (-10, -6, -10) and (-14, -18, -6). Testing at (6, -6, -6) showed activation at (10, -12, -8) and testing at (-6, -6, -6) showed activation at (-6, -12, -8). There was no significant negative activation on binary analysis.

Patient #23- SUNCT- attacks on both sides

On binary analysis there was positive activation bilaterally in the posterior region, and in the right anterior region. Testing at (6, -16, -6) showed activation at (4, -12, -14) (**Figure 12.15**), (6, -8, -10) and (10, -16, -2). Testing at (-6, -16, -6) showed activation at (-12, -16, -10) (**Figure 12.16**). Testing at (6, -8, 0) showed activation at (-2, -10, 0), (6, -8, -10) and (8, -6, 0) (**Figure 12.17**). Testing at (6, -6, -6) showed activation at (4, -10, -14), (6, -8, -10) and (8, -6, 0).

On parametric analysis there was positive activation bilaterally in both posterior and anterior regions. Testing at (6, -16, -6) showed activation at (4, -12, -14). Testing at (-6, -16, -6) showed activation at (-12, -16, -10). Testing at (6, -8, 0) showed activation at (8, -6, 0), but testing at (-6, -8, 0) showed activation at (-2, -2, 6) (**Figure 12.18**). Testing at (6, -6, -6) showed activation at (6, -12, -14), and (8, -6, 0).

Patient #33- SUNCT- right sided attacks

There was no significant positive activation on either binary or parametric analysis. However there was right-sided posterior and anterior negative activation in both binary and parametric analysis. Testing at (6, -16, -6) showed activation at (6, -4, -6) for parametric and (16, -14, -6) for binary analysis. Testing at (6, -8, 0) and (6, -6, -6) showed the same results: activation at (6, -4, -4) for parametric analysis, and (6, -2, -4) and (6, -4, -8) for binary analysis (**Figure 12.19**).

Figures 12.15 and 12.16

Positive activation bilaterally in the posterior region in patient #23

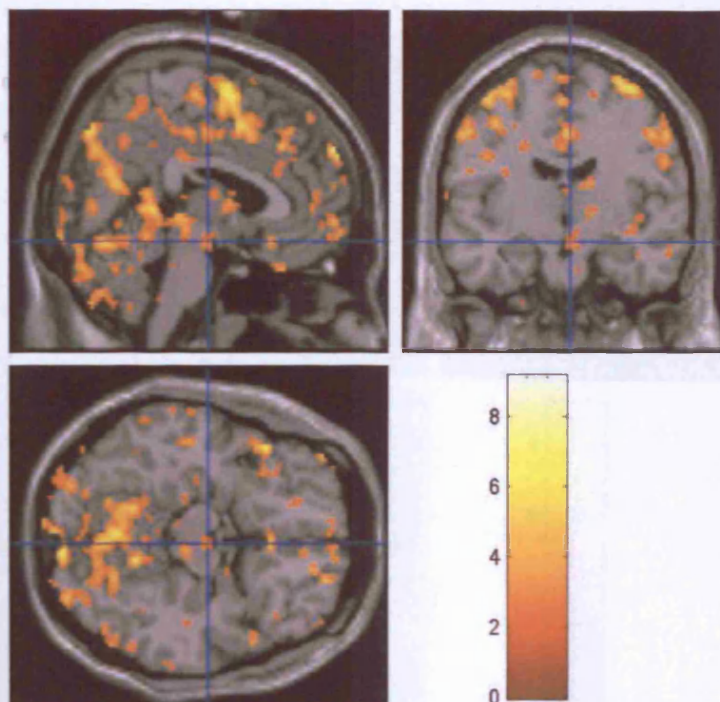


Figure 12.15
Positive activation at (4, -12, -14)

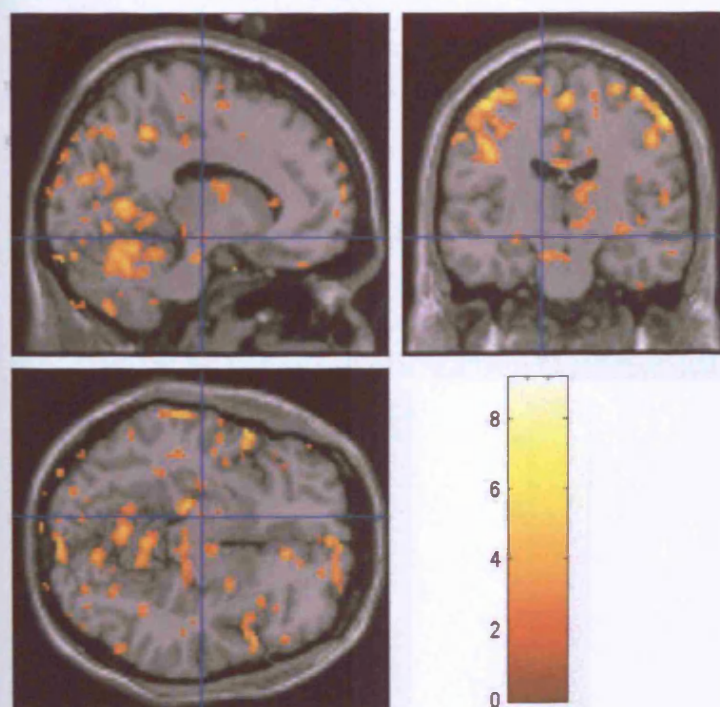


Figure 12.16
Positive activation at (-12, -16, -10)

Figures 12.17 and 12.18

Positive activation in anterior regions in Patient #23

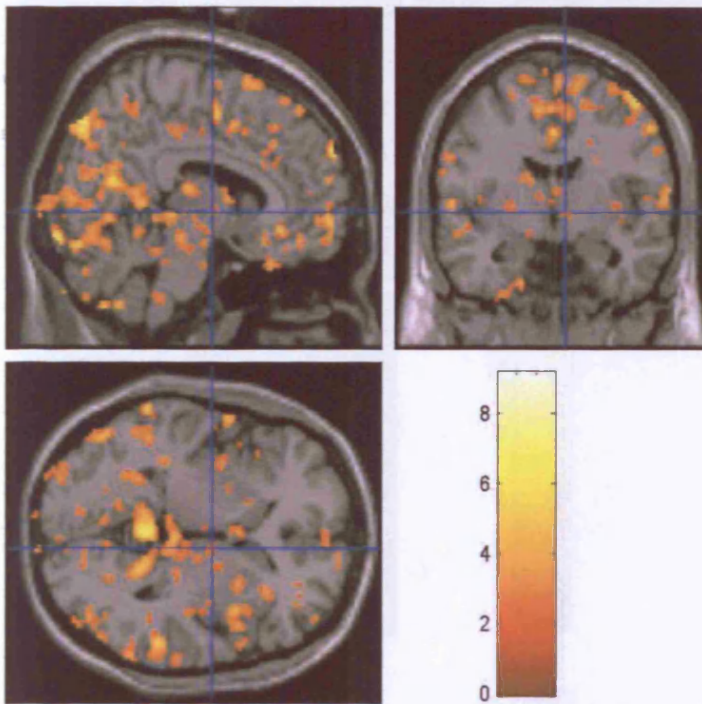


Figure 12.19

Positive activation at (8, -6, 0)

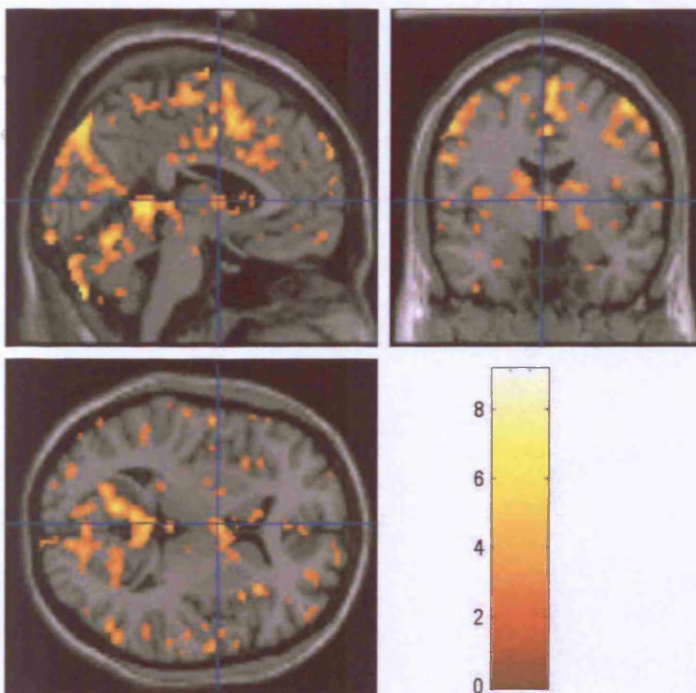


Figure 12.18

Positive activation at (-2, -2, 6)

Figure 12.19
Ipsilateral negative activation in patient #33

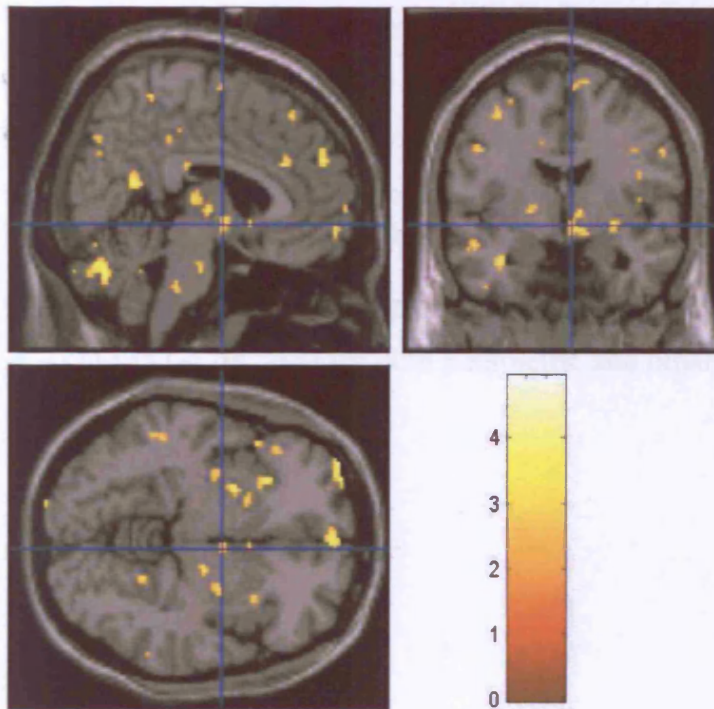


Figure 12.19
Negative activation at (6, -4, -8)

Patient #34- SUNCT- left sided attacks, left sided cluster headache, and migraine

There was significant positive activation in both anterior and posterior regions, on both sides. This was in both binary and parametric analyses. Testing at (6, -16, -6) showed activation at (10, -8, -12) (**Figure 12.20**) and (2, -14, -14). Testing at (-6, -16, -6) showed activation at (0, -14, -14) for both parametric and binary analysis, and also at (-2, -10, -14) for parametric analysis (**Figure 12.21**). Testing at (6, -6, -6) showed activation at (10, -6, -14) and (6, -2, -12) (**Figure 12.22**). Testing at (-6, -6, -6) showed activation at (-12, -6, -14) and (-4, -4, -14) for both parametric and binary analysis, and also at (-2, -10, -14) for parametric analysis.

Figures 12.20 and 12.21

Positive posterior activation in Patient #34

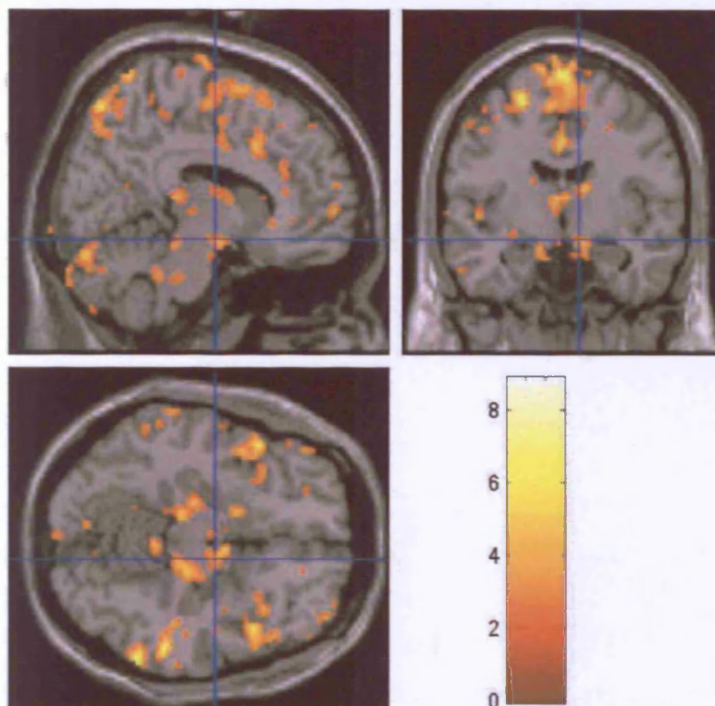


Figure 12.20
Positive activation at (10, -8, -12)

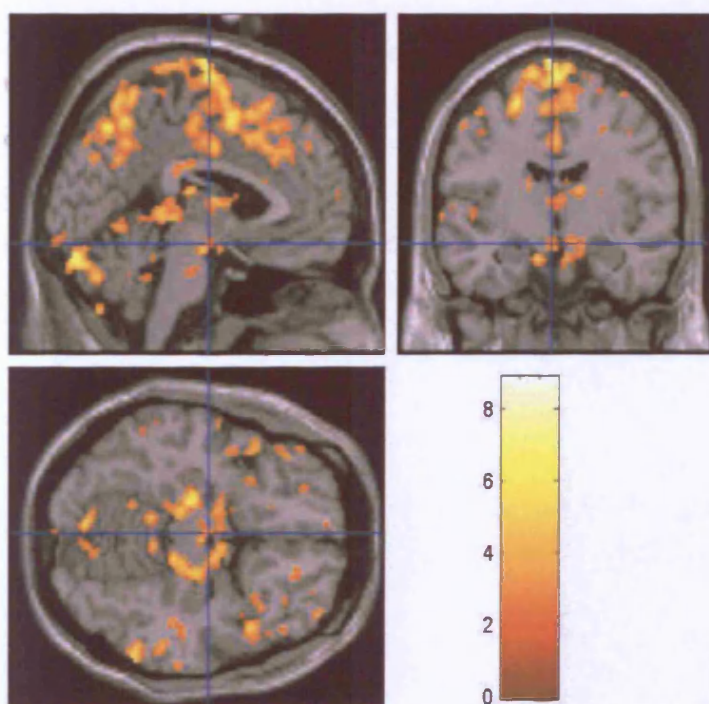
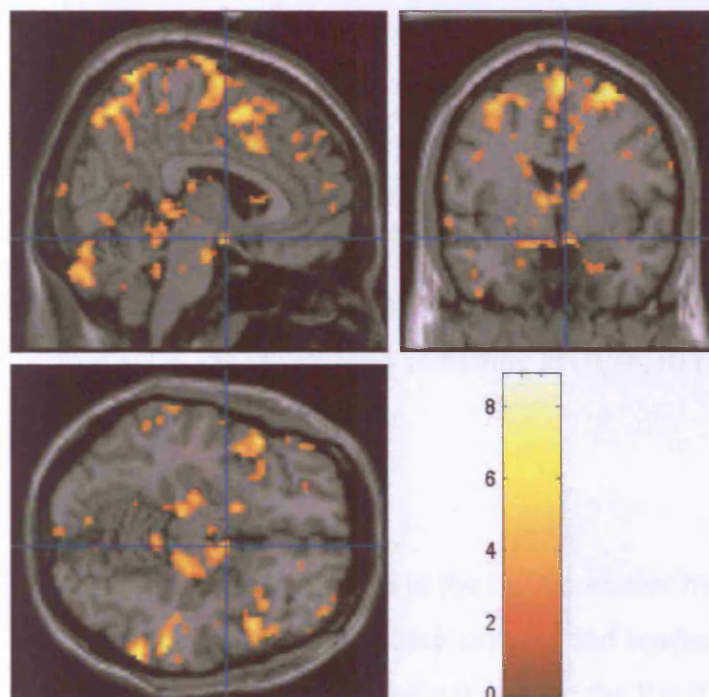


Figure 12.21
Positive activation at (-2, -10, -14)

Figure 12.22

Positive anterior activation in Patient #34

**Figure 12.22**

Positive activation at (6,-2,-12)

12.3 Group Results

Fixed effects analysis

On assessing the binary pain states (attack on/off). There was significant positive activation in the anterior and posterior regions of the hypothalamus bilaterally on fixed effects analysis. Testing at (6, -16, -6) showed activations at (6, -22, 2), (2, -12, 2) and (2, -8, -2). Testing at (-6, -16, -6) showed activation at (-6, -24, 0), (2, -12, 2), (-14, -18, -2) and (-2, -8, -2) (**Figure 12.23**). Testing at (6, -6, -6) showed activation at (4, -4, 2). Testing at (-6, -6, -6) showed activation at (0, -6, 0) (**Figure 12.24**). There was no significant negative activation.

Random effects analysis

There was positive activation in the right posterior hypothalamic region on analysing both the binary pain states (attack on/off), and headache parametrically analysed with pain severity. However this did not survive the $P \leq 0.001$ threshold for significance. There was no significant negative activation.

12.4 Group Analysis- no *a priori* hypothesis

There was positive activation in 21 clusters of voxels, all of which survived the threshold of $P < 0.05$ uncorrected for whole brain. These included bilateral primary somatosensory cortices, bilateral insulae (**Figure 12.25**), bilateral orbitofrontal cortices, the mediodorsal thalamic nucleus on both sides (**Figure 12.26**), right anterior cingulate cortex, right primary motor cortex incorporating left cingulate gyrus, right occipital cortex, left middle occipital lobe incorporating left temporal lobe, left putamen/globus pallidus, bilateral superior parietal cortex, and bilaterally in the cerebellum. These results are shown in Table 12.2.

There was no significant negative activation.

Figures 12.23 and 12.24
Positive activation in group analysis (fixed effects)

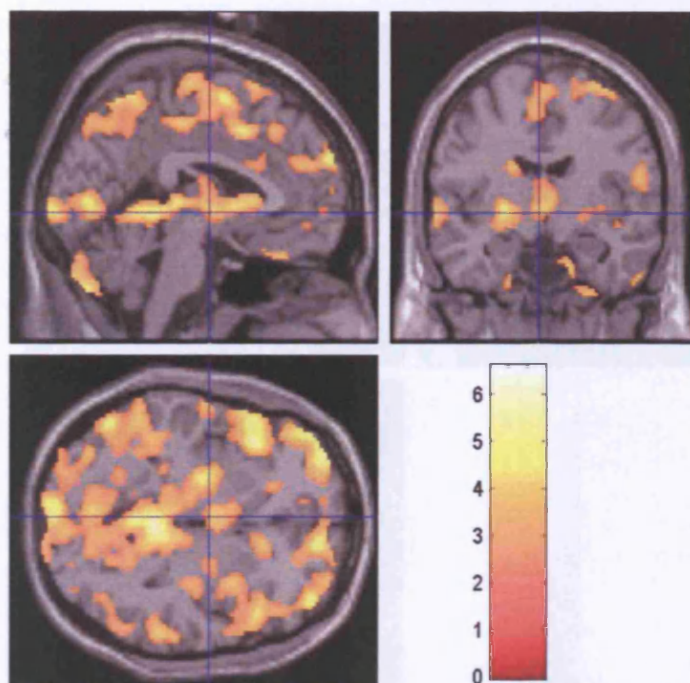


Figure 12.23
Positive activation at (-2, -8, -2)

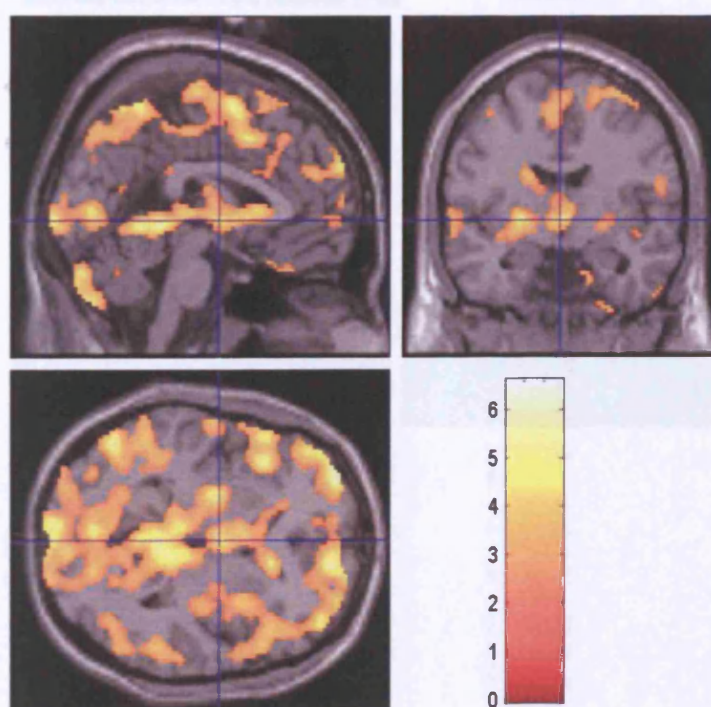


Figure 12.24
Positive activation at (0, -6, 0)

Figures 12.25 and 12.26

Activation on group analysis with no *a priori* hypothesis

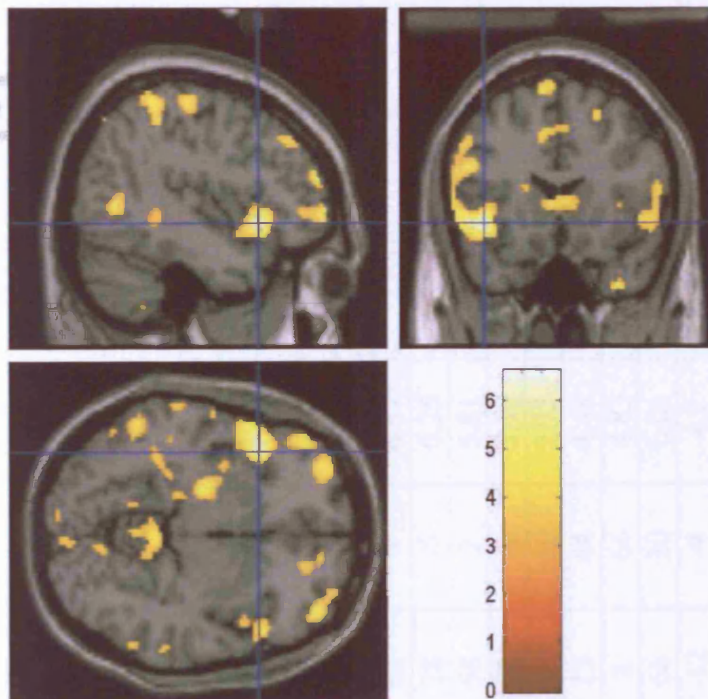


Figure 12.25

Positive activation in the insula:
on the right side at (52, 20, -4) and
on the left side at (-42, 18, -6)

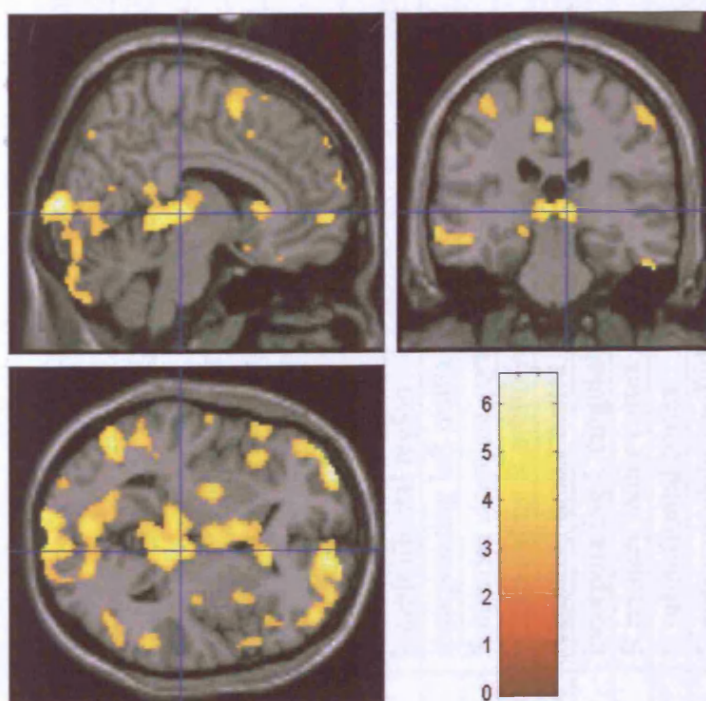


Figure 12.26

Positive activation in the
mediodorsal thalamic nucleus: on
the right side at (8, -26, 2) and on
the left side by inspection at (-8, -
26, 2)

Table 12.2Activations in group analysis for whole brain with no *a priori* hypothesis

cluster	location	coordinates (mm)			Z score	voxel size
		x	y	z		
1	R primary somatosensory cortex	50	-32	54	5.67	334
2	L primary somatosensory cortex	-36	-48	60	5.14	354
3	L primary somatosensory cortex	-32	-16	64	4.84	289
4	R prefrontal cortex	52	32	20	4.76	481
	incorporating R insula	52	20	-4	4.49	
5	L orbitofrontal region	-30	62	4	6.57	2520
	incorporating left insula	-42	18	-6	6.25	
6	R anterior cingulate cortex	14	58	2	5.81	656
	incorporating R orbitofrontal cortex	44	52	-2	5.16	
7	R primary motor cortex	4	4	60	5.73	582
	incorporating L cingulate gyrus	-2	12	44	4.49	
8	R primary motor cortex	26	2	66	4.83	264
9	R orbitofrontal cortex	16	66	20	6.01	160
10	L putamen/globus pallidus	-22	-12	-4	4.9	220
11	R superior parietal cortex	16	-74	52	4.57	226
	incorporating L parietal lobe	-2	-66	46	3.45	
12	midline posterior parietal cortex	0	-52	62	4.68	142
13	L middle occipital lobe	-50	-66	2	5.52	684
	incorporating L superior temporal lobe	-68	-30	-8	4.19	
14	R occipital cortex	8	-96	8	6.53	1836
	incorporating L occipital cortex	-10	-106	-8	5.55	
15	R occipital lobe	32	-76	12	5.03	183
16	R occipital lobe	50	-60	-24	4.76	186
17	R occipital lobe	46	-66	6	4.46	158

Table 12.2 ctd

18	L cerebellum	-26	-64	-30	4.14	289
19	R cerebellum	44	-78	-38	4.57	203
20	R cerebellum	24	-58	-28	4.47	195
21	R cerebellum	4	-40	-2	5.91	1580
	incorporating mediodorsal thalamic nucleus	8	-26	2	5.38	

Chapter 13

Discussion: Functional MRI in attacks of SUNCT and SUNA

13.1 Results from this series

Bilateral Activation

Some patients (#7, #12, #17, and #34) had left-sided attacks but bilateral positive activation in the posterior region. In their cases, the bilateral activation may indicate a propensity for TACs on both sides but which are clinically manifest only on one side at present. For patient #7 this is unsurprising as he could have attacks on either left or right side, but had only left sided attacks during the scanner. Another patient (#34) had experienced some attacks on the right side in the past, but none during the scanning session.

Bilateral Attacks

One patient (#23) had attacks in the scanner affecting either left or right side in equal proportions, and had significant activation bilaterally in both anterior and posterior hypothalamic regions.

One patient (#7) experienced only left-sided attacks during the scanning session, but could experience right-sided attacks at other times. This could be that even though only the left sided attacks were manifest during the scanning session, there was still bilateral hypothalamic activation and the patient had the potential to experience right-sided attacks as well.

Unilateral Attacks

Two patients (#42 and #56) had left sided attacks with right-sided posterior hypothalamic activation.

Patients with right-sided attacks (#6, #33) had negative right-sided activation, although this was more anterior in patient #33. This negative activation may represent a reciprocal inhibition, such that in unilateral syndromes, when one side is active, the other side has an opposite effect. Patient #42 also had negative anterior activation which was bilateral.

SUNA

Both SUNA patients had negative activation. Patient #SUNA40 had right-sided SUNA attacks. His activation was ipsilateral in the posterior region and bilateral anteriorly. In the second SUNA patient (#SUNA44) there was bilateral negative activation with only left-sided attacks.

In both patients the bilateral activation could be explained as a propensity for them to develop bilateral attacks. Indeed Patient #SUNA40 had a TAC on the left side which was not assessed in this analysis. However the striking finding is that both SUNA patients had only negative activation. This raises the possibility that SUNA has a different pathophysiological basis to SUNCT, in that the hypothalamus is activated differently in the two conditions (i.e. positive in SUNCT and negative in SUNA). This in turn may modulate the autonomic and nociceptive pathways differently between the two syndromes via the disinhibition of the trigeminal-autonomic reflex (Benjamin et al., 2004) and the hypothalamic-trigeminal pathway (Bartsch et al., 2004; Malick and Burstein, 1998), which may account for the lack of conjunctival injection and lacrimation as autonomic symptoms in SUNA.

Symptomatic SUNCT

The patient with symptomatic SUNCT (#2) had no significant activation in the region of the anterior or posterior hypothalamus, either in binary analysis or with headaches assessed parametrically with pain ratings. It may therefore be fair to speculate that patients with symptomatic SUNCT/SUNA which are secondary to intracranial lesions have a different pathophysiology to those with the idiopathic disease. However there was some subthreshold posterior hypothalamic activation which did not survive significance. Moreover this is just a single case so it would be difficult to generalise to other cases,

especially those with SUNCT/SUNA secondary to lesions elsewhere in the brain. Furthermore, the patient had a very abnormal structural MRI scan with an unusual configuration of the deep grey matter at the lateral ventricles and the upper brainstem, and a lacune in the left thalamus. Whereas the normalisation step in pre-processing should be able to warp the brain onto a standard template, even with inter-subject variations in structural scans (Friston et al., 1995a), this patient's abnormalities may have eluded even the normalisation processes of SPM, and would therefore have given results of a diminished quality.

13.2 Location of the hypothalamus

The functional imaging studies done hitherto have reported activation in the area of the posterior hypothalamus (for example, (± 6 , -14, -6) (Matharu et al., 2004c) and (± 2 , -18, -8) (Leone, 2001; May et al., 1998a; May et al., 2000)), but also in the anterior region of the hypothalamus, especially in SUNCT and the atypical TAC (Cohen et al., 2004a; Sprenger et al., 2004b; Sprenger et al., 2005), as illustrated in Table 11.2. The reporting here of slightly different coordinates for the hypothalamus may be explained in the following way:

- 1) There may be a difference in the exact location of the hypothalamic activation between different syndromes. This was raised in light of the atypical TAC which had activation at different coordinates to CH (Sprenger et al., 2004b). However the argument against this would be activation of the posterior region in all TACs and HC, and its response to stimulation in CH and SUNCT.
- 2) Different scanning techniques, smoothing parameters and statistical analyses between authors may contribute to slightly different voxels. In this study the smoothing kernel was 4mm at FWHM (full width half maximum) for individual cases, and an 8mm sphere was used for the region of activation, although this was by no means standard across the studies.
- 3) In cases of bilateral activation, the coordinates were different for ipsilateral ($x, y, z = 9, -9, -6$) and contralateral hypothalamus in the same patient ($x, y, z = -6, -6, -6$)

(Sprenger et al., 2005); so the reported active voxels may vary from one side to another even within the same patient.

- 4) The coordinates for stimulation varied between studies, and even within stimulation series. For instance Leone *et al* (Leone, 2001) started with one set of coordinates with a good outcome, and then changed them after 2 patients when they realised there was a better outcome with the more anterior coordinates (Franzini et al., 2004). Schoenen and colleagues (Schoenen et al., 2005) used the older, more posterior coordinates and found more oculomotor side effects and a need for higher stimulation. This suggests that the area stimulated may have been just outside the hypothalamus.
- 5) A study showing correlation of functional and structural changes in patients with CH (via fMRI and VBM respectively), demonstrated activation at the hypothalamus at slightly different voxels: (-2, -18, -8) for functional imaging and (-4, -16, -10) for VBM changes (May et al., 1999a). This (albeit small) difference serves to highlight the inexact nature of pinpointing the posterior hypothalamus, even using different techniques within the same group of patients. Therefore an 'area in the region of the posterior hypothalamus' is implied, and the imaging data with a smoothing kernel of up to 10mm is accepted as such.

It is the anterior regions which are conventionally described as the hypothalamus (Talairach and Tournoux, 1988). However it seems to be the posterior regions that respond to surgical intervention, both in terms of attacks and also for the agitation associated with the attacks (Sano et al., 1970), which is a known feature of TACs, as discussed in Section 5.9. There may be a number of reasons for the discrepancy, which is borne out by our study:

- 1) There may be activation or deactivation both of the posterior and anterior regions, as in patients #SUNA40, 6, 12, 17, 23 and 34. This activation may have not survived significance testing in all patients.

- 2) There may be posterior activation with reciprocal anterior hypothalamic deactivation such as in patient #42. It is unclear from previous studies with posterior positive activation whether they checked for anterior negative activation.

13.3 Negativity

The advantage of the T test is that directions of activation (*e.g.* activation or deactivation) can be studied (Josephs and Henson, 1999). In a number of our subjects the activation was negative; that is a Z score > 2.99 was obtained at $P < 0.001$ uncorrected with a negative T -test at that voxel. Negative activation has been reported in the posterior cingulate cortex in PET (Coghill et al., 1994), and subthreshold negative signal changes in the hypothalamus in fMRI studies of pain (Becerra et al., 1999). An area of deactivation in the ipsilateral pons, alongside activation in the contralateral pons, has been reported in spontaneous migraine (Afridi et al., 2005b). The role of negativity in functional imaging studies remains unclear; it could be due to decreasing neural activity at that site or synaptic inhibition by GABAergic interneurons (Lauritzen and Gold, 2003), although the release of inhibitory neurotransmitters is an energy-demanding process in itself which may evoke increases in rCBF (Coghill et al., 1994; Sokoloff, 1991).

In one patient (#42) there was positive activity on the right side and negative activity contralaterally, and in two patients with right sided attacks (#6 and 33) there was negative right-sided activation. This suggests a reciprocal activation and deactivation across the midline, in that activation associated on the side contralateral to the headache is accompanied by deactivation on the other side. This phenomenon has been reported in the pons in a PET study of migraine (Afridi et al., 2005b). In the two patients with right-sided attacks the activation which should have been seen on the left side may not have survived the threshold for significance.

13.4 Laterality

One of the prerequisites of SUNCT by definition is unilaterality. However this study shows eight patients with SUNCT who have either right- or left-sided attacks, and one with bilateral attacks, in Chapter 5.4. Three of these patients participated in the fMRI study. These were #7 who had exclusively left-sided attacks during the scanning session although he had right-sided attacks on other occasions, and #23 whose attacks were equally distributed between right and left. The third patient (#34) usually had left-sided attacks, but had very occasionally experienced SUNCT attacks on the right side. Bilateral attacks of SUNCT have been reported in isolated cases (Kuhn et al., 2005; Pareja and Sjaastad, 1997; Sabatowski et al., 2001).

A study by Afridi *et al* (Afridi et al., 2005c) specifically aimed at assessing lateralisation of activation in migraine, found ipsilateral dorsolateral pontine activity in unilateral attacks, but patients with bilateral migraine activated the left side of the dorsolateral pons predominantly, and a conjunction analysis revealed that in fact there were bilateral activations. The authors speculated that the activation could have spread to the contralateral side during the course of the attack, as is the case in cutaneous allodynia (Burstein et al., 2000), or that the unilateral pain could result from an asymmetric brain dysfunction.

Bilateral hypothalamic activity during unilateral attacks of SUNCT has been previously reported in 2 patients in this series (Cohen et al., 2004a), and in a third patient with cutaneously triggered attacks (Sprenger et al., 2005). It is noted that in all 3 patients this was the anterior aspect of the hypothalamus which was active. Previously hypothalamic action has been described as *ipsilateral* to the side of the pain in SUNCT (May et al., 1999b), triggered cluster headache (May et al., 1998a; May et al., 2000), a spontaneous CH attack in which a hypothalamic stimulator had been implanted and then switched off (Sprenger et al., 2004a), but *contralateral* in PET studies of paroxysmal hemicrania (Matharu et al., 2006b) and hemicrania continua (Matharu et al., 2004c).

The striking feature of TACs is the unilaterality of their attacks, as reinforced by unilateral photophobia and phonophobia in 48-80% of patients with TACs and hemicrania continua but only in 4-13% of migraine patients (Irimia et al., 2005). However the functional imaging results suggest that the pathophysiology is a bilateral issue. Indeed, most primary headache syndromes can involve bilateral pain. For example, migraine, which derives its name from the term *hemicrania* since Galen (AD131-201) (Lance, 1998), can be bilateral, and hemicrania continua can alternate sides (Marano et al., 1994; Matharu et al., 2006a; Newman et al., 1992; Newman et al., 2004). Cluster headache can also occur with side shifts between bouts, between attacks, and during attacks (Bahra et al., 2002), and has rarely been reported as affecting both sides at the same time (Kudrow, 1980; Sjaastad et al., 1985; Young and Rozen, 1999). It is known to recur on the opposite side to trigeminal gangliorhizotomy (Mathew and Hurt, 1988) in patients with a past history of attacks on that side; and in a recent series of trigeminal nerve section in CH, 2 patients with no history of contralateral attacks developed CH on the opposite side to the trigeminal root section (Jarrar et al., 2003).

In terms of deep brain stimulation, a total of sixteen CH patients with ipsilateral posterior hypothalamic stimulators had relief of their symptoms (Franzini et al., 2003; Leone et al., 2004b), and a SUNCT patient had successful ipsilateral posterior hypothalamic stimulation (Leone et al., 2004b). Six cases of ipsilateral ventroposterior hypothalamic stimulation have been published with two patients painfree (Schoenen et al., 2005). In two patients with bilateral CH ipsilateral stimulators only provided relief in the ipsilateral side, and therefore had bilateral stimulators implanted with good effect (Leone et al., 2003b; Leone et al., 2004a). One of these patients had headache recur on the opposite side despite destructive trigeminal surgery to that side, thus providing further evidence that TACs are indeed centrally generated syndromes and are not purely peripheral nerve phenomena.

Occipital nerve stimulation has been used in patients with bilateral chronic migraine, who received bilateral stimulators with a marked beneficial response (Matharu et al., 2004a). They have also produced a fair to excellent outcome in 2 patients with CCH, 2 with

chronic migraine and one with hemicrania continua (Dodick et al., 2005). However unilateral occipital nerve stimulation in 5 patients with CCH provided no lasting relief in 4 patients, and caused the headache to recur on the contralateral side in the fifth patient (Magis et al., 2005). The side switch may be explained by a bilateral predisposition to develop a TAC, which is manifest only on one side and remains subclinical on the opposite side until the first side is suppressed.

The apparent discrepancy in laterality of activity observed in this series may be due to a number of reasons:

- 1) The first is that the hypothalamus has abnormal activity on the side contralateral to the attacks (as in patients #42 and #56): the other side is either inhibited (as in patients #6 and #33), or there is activation of inhibitory neurons in order to compensate for the abnormal activity.
- 2) The second reason is that either side of the hypothalamus can generate attacks on either side of the face, as being a midline structure it is not generally associated with a lateralized hemibody function in hormonal or other functions. This may be the case in Patient #7, for whom analysis in both left and right posterior regions showed activation which straddled the midline (Figure 12.5).
- 3) Moreover there are bilateral projections from each side of the hypothalamus to the caudal trigeminal nucleus and brainstem parasympathetic nuclei, and this may explain why a unilateral lesion of the trigeminal sensory pathway does not exclude the possibility of contralateral trigeminal and parasympathetic pathways being recruited by a rostral diencephalic generator (Malick and Burstein, 1998).
- 4) Another explanation could be in the nature of SUNCT/SUNA attacks; the stab attacks are very short-lasting (1-600 seconds in this series), and therefore the switch between hypothalamic activation and deactivation may also be in this time frame. An activation on one side and contralateral deactivation may flip so quickly, especially in saw-tooth attacks (Figure 5.3), that the overall picture may be one of bilateral activation.

13.5 Hypothalamic activity as a cause or consequence of trigeminal pain?

One may argue that the activations seen in the hypothalamic region may be secondary to the pain of the SUNCT/SUNA attacks, and not a generator of the attacks. This theory can be refuted by a study which applied painful electrical stimuli to the first division of the trigeminal nerve, and found activation in the insula, thalamus, somatosensory cortex, and cingulate cortex, but not in the hypothalamus (Fitzek et al., 2004). Moreover the hypothalamus is implicated as a generator for these attacks by virtue of the striking autonomic symptoms in SUNCT/SUNA, which are thought to be due to hypothalamic-autonomic reflexes (Goadsby et al., 2001). Moreover agitation is seen in SUNCT and TACs (Chapter 5.9), and is resolved by destruction or stimulation of the posterior hypothalamic region (Franzini et al., 2005; Sano et al., 1970). Furthermore posterior hypothalamic stimulation was performed on one SUNCT patient with a beneficial effect (Leone et al., 2005), thus suggesting that this region is a generator or modulator of the attacks.

13.6 Hypothalamic activity and clinical characteristics

Some patients had contralateral posterior hypothalamic activation in SUNCT (Patients # 42, 56), some had reciprocal ipsilateral deactivation (patients # 6, 33), and some patients with attacks that were not strictly unilateral had bilateral positive activation (#7, 23, 34). Two patients (#12, #17) had bilateral activation but unilateral attacks. In SUNA, we can assume negative activation, which is bilateral in both cases. The only patient with no significant activation was one with SUNCT secondary to a brainstem lesion (#2).

The clinical characteristics of these patients, and their responses to medications, were explored in the light of the fMRI findings. These are tabulated in Table 13.1.

Table 13.1
Hypothalamic activity and clinical characteristics in SUNCT and SUNA

Patient no and diagnosis		side	activations		LTG response	TPM response	awake/asleep	photo/phonophobia	migraine biology	background pain	triggers	episodic or chronic disease
			location	polarity								
2	Symptomatic SUNCT	R	nil		+	++	both	phonophobia	0	1	none	chronic
SUNA44	SUNA	L	bilateral posterior	neg	-	-	both	none	1	0	none	chronic
SUNA40	SUNA and TAC	R	contralateral posterior and bilateral anterior	neg	-	n	awake, early morning	ipsilateral photophobia	1	0	none	chronic
6	SUNCT	R	ipsilateral anterior and posterior	neg	++	n	awake	nausea	0	0	most	secondary chronic
7	SUNCT	L (bilat)	bilateral posterior	pos	+	-	both	nil	0	1	few	chronic
12	SUNCT	L	bilateral posterior and left anterior	pos	+	-	both	ipsilateral photophobia, bilateral phonophobia	0	1	few	chronic
42	SUNCT	L	contralateral posterior	pos	++	++	both	nausea, ipsilateral photophobia	1	0	equal	chronic
			bilateral anterior	neg								
56	SUNCT	L	contralateral posterior	pos	-*	++	awake	nausea	0	1	most	secondary chronic
17	SUNCT	L	all	pos	++	-	both	nil	1	1	equal	chronic
23	SUNCT	bilateral	all	pos	++	n	awake	ipsilateral photophobia	0	0	none	chronic
33	SUNCT	R	ipsilateral anterior and posterior	neg	-	n	awake, early morning	nil	1	0	most	episodic
34	SUNCT, migraine and CH	L	all	pos	-	-	unsure	bilateral phonophobia	1	1	none	chronic

Key: all = bilateral posterior and anterior, pos = positive activation, neg = negative activation, LTG = lamotrigine, TPM = topiramate, + = moderate effect, ++ = good effect, - = no effect, -* = no effect at low dose which had to be stopped due to side effects, n = not tried, awake/asleep = diurnal variation of attacks occurring mainly during waking hours or sleep

There was no obvious link between clinical characteristics and activation, other than the diagnosis of idiopathic SUNCT, symptomatic SUNCT or SUNA.

Triggering of attacks

One patient with SUNCT (#17) whose attacks were triggered for the scanner, had bilateral positive activation. This would strengthen the importance of hypothalamic-trigeminal connections in SUNCT; given the fact that the patient's attacks (and hypothalamic activation) persisted long after the stimulus was removed, it is possible that the hypothalamus is switched into an active state for a short while following a trigeminal cutaneous trigger. One could assume that attacks that were mostly triggered would have a different hypothalamic activation to spontaneous attacks, via the hypothalamic-trigeminal pathway and the hypothalamic modulation of autonomic symptoms. Therefore it might be speculated that SUNA with its relative paucity of V_1 autonomic symptoms and relative lack of triggerability would explain the negative hypothalamic activation. Indeed both SUNA patients had attacks that were entirely spontaneous, as has been shown to be more common in SUNA than SUNCT (Table 5.12). However two SUNCT patients with entirely spontaneous attacks (#23 and #34) had bilateral positive activation as opposed to the negative activation found in SUNA. Therefore no correlation can be made between triggerability of attacks and patterns of activation.

Previous studies in SUNCT have assessed triggered attacks, and have found ipsilateral (Sprenger, 2004) or bilateral (Sprenger et al., 2005) hypothalamic activation, although the coordinates specified were rather more anterior. Ipsilateral activation was demonstrated in spontaneous SUNCT attacks (May et al., 1999b) in the region of the posterior hypothalamus. It may be, therefore, that triggered attacks are associated with anterior hypothalamic and spontaneous attacks with posterior hypothalamic activity. Some patients with equal or predominantly triggered attacks had anterior hypothalamic activation (#6, 42, 17, 33). However there were patients with entirely spontaneous attacks whose activation was anterior as well (#23, 34). We would therefore conclude that both triggered and spontaneous attacks are associated with either anterior or posterior hypothalamic activation, or both.

Diurnal variation of attacks and migrainous features

Given that the hypothalamus is known to regulate circadian (and seasonal) rhythms, through the suprachiasmatic nucleus (SCN) (Ralph et al., 1990), and that cluster headache has a strong diurnal variation, with attacks occurring at specific times of day or usually during the night (Bahra et al., 2002; Russell, 1981), it might be expected that SUNCT patients with a similar pattern of hypothalamic activity to CH would exhibit similar diurnal variation of attacks. However there was no discernible pattern in activation in patients whose attacks occurred with a predominantly diurnal variation, as would be expected in hypothalamically-driven attacks.

Migraine biology and migrainous features

Patients with migraine biology (the two SUNA patients, #42, 17, 33, 34) had no unifying pattern to their activation, nor did those with background interictal pain (#2, 7, 12, 56, 17, and 34). Interestingly, both patients with bilateral phonophobia associated with their attacks (#12, #34) also had bilateral positive activation. Usually TACs have unilaterality of symptoms such as photophobia and phonophobia (Irimia, 2005), so the presence of bilateral phonophobia in association with bilateral positive activation might indicate the propensity of these patients to develop bilateral attacks. Alternatively this may be a manifestation of bilateral representations of central structures such as the hypothalamus in unilateral attacks.

Response to treatments

It would be attractive to speculate that lamotrigine and topiramate targeted the hypothalamus; thus by suppressing attacks they would prevent not just the pain, but also the accompanying autonomic symptoms and agitation that are attributed to hypothalamic activation. However there were no obvious links between responses to preventives such as lamotrigine and topiramate, and hypothalamic activation. This could be due to the small number of patients in the fMRI study, and of these one patient (#56) could only tolerate a low dose of lamotrigine due to its side effects. Indeed the patient with symptomatic SUNCT (#2) with no significant hypothalamic activation demonstrated, had a moderate to good response to both lamotrigine and topiramate.

13.7 Pain, verbal rating scales and linearity

The assessment of level of perceived pain is important, not only for research purposes, but also in order to gauge the response to treatment. Pain is a multi-dimensional phenomenon, including nociceptive intensity, affective components, and cognitive aspects related to the pain. The pain intensity or severity is the aspect most commonly measured in pain (Von Korff et al., 2000); usually by a continuous visual analogue scale (VAS) or discrete categories such as in the verbal rating scale (VRS) or numerical rating scale (NRS). The NRS had previously been reported as preferable for chronic pain syndromes (Dworkin et al., 2005), and although no one scale has proven superior in showing benefits associated with treatment of pain, patients tend to prefer NRS or VRS scales as they are easier to understand (Jensen, 2001), and a greater intra-individual concordance was found using VRS rather than the continuous VAS scale (Lund et al., 2005).

The pain intensities on the VRS, by nature of being descriptive (no pain, mild, moderate and severe), are transferable to a linear scale (0, 1, 2 and 3 respectively) but this may not reflect a true proportionality of the pain experience. However Lund et al (Lund et al., 2005) found that it was particularly the VAS scale particularly did not show linearity with the pain intensity assessments. Linearity has been demonstrated in NRS scales, but only in certain conditions such as obstetric and postoperative pain, and not for postoperative orthopaedic patients (Hartrick, 2003). The authors concluded that the young age of the former group and the nature of the visceral pain may account for the differences.

In fMRI, the magnitude of the BOLD response is assumed to be linearly related to the magnitude of underlying neuronal activity (Josephs and Henson, 1999). It has previously been shown that signal changes at the ACC correlated with the intensity of the pain (Davis et al., 1997).

Functional imaging studies of pain have assessed pain-related activation in different ways. Some studies use a separate analysis each for painful and non-painful stimuli, and then performed a *T* test between the groups at the region of interest (Becerra et al., 1999). Others perform separate analyses per pain intensity unit (on a verbal rating scale from 0 to 10) in visceral pain (Dunckley et al., 2005a), and multiple regression analyses were used to assess the effect of different intensities of arm pain (Coghill et al., 1999). A recent fMRI study used a four-point scale ranging from no pain to severe pain, and modelled the haemodynamic response in a linear parametric conjunction analysis in order to determine the stimulus intensity-related effects at the anterior cingulate cortex (ACC) (Mohr et al., 2005).

There are however a number of differences between measuring pain in SUNCT patients for fMRI and other scenarios. One is that outcome measures for pain clinical trials usually deal with conditions such as osteoarthritis and low back pain; these are constant or long-lasting painful episodes wherein the pain levels may vary during an episode of pain, as opposed to the short-lasting neuralgiform attacks of SUNCT and SUNA which are usually separated by pain-free periods and may in some cases be too short for a perceptible intra-attack change in pain rating.

The difference in functional imaging terms is that studies so far have focused on the CNS response to a graded painful stimulus. The hypothesis in this study is the reverse: that there is hypothalamic activation which causes the attacks, and that a greater activation may cause a greater degree of pain in the attack. Aside from two patients whose results have been reported in 2004 (Cohen et al., 2004a), this aspect of differential hypothalamic activation in primary headache syndromes has not been explored.

13.8 Shortcomings of the Study

Location of hypothalamus

As it can be seen from the figures, (for example Figures 12.10 (Patient #56) and 12.18 (Patient #23)), some of the activations shown are in clusters of activated voxels which do not correspond to the area generally regarded as the posterior aspect of the hypothalamus in previous imaging work (Table 11.2). Furthermore some patients have activation which has been reported as bilaterally positive, when the cluster of activated voxels has straddled the midline (Patients #7, 17, 42, SUNA44). However we have reported these as positive results, due to the *a priori* hypothesis for the study, which specified the region of the posterior hypothalamus as a spherical region of interest with radius 10mm. Any activated voxels within this region which met the threshold of $P \leq 0.001$ (uncorrected) were therefore included in the analysis.

Small numbers

Some patients only had a small number of attacks (#7, #33, #SUNA44); therefore the rate of detection of activation may have been diminished. However the SPM package provides a statistically robust method, so any activation with $P \leq 0.001$ in an individual patient was reported.

Methodological Issues

During the scanning sessions, the patients received an auditory tone once every 3.96 seconds, which prompted them to rate their pain via a keypad. The design matrix was constructed such that each headache 'event' was the 3.96 seconds between consecutive tones. Attack lengths were therefore calculated as the number of positive keypresses multiplied by 3.96 seconds. It is possible that an attack could be shorter than 3.96 seconds, or could have started or terminated in the middle of one of these epochs, and this information would be missed according to the current paradigm. However the haemodynamic response function, that is the transient increase in regional cerebral blood flow cause by neuronal activity, has been estimated at around 5 seconds (Friston et al., 1995b), and the BOLD signal which is roughly proportional to the concentration of

deoxyhaemoglobin, follows the rCBF function with a delay of about 1 second (Friston, 2003), so any events taking place on a shorter timescale than this may not be accurately modelled by the GLM.

One problem with this design matrix is that the start of each headache event was timed to the onset of the auditory stimulus. As the neuronal activity associated with 'sound' had to be modelled out in the design matrix, it is possible that some information from each headache event was lost. In order to minimise any loss of information, the 'sound' and 'keypress' functions were modelled as events lasting zero seconds each, and the 'headache' event lasted 3.96 seconds.

Medications

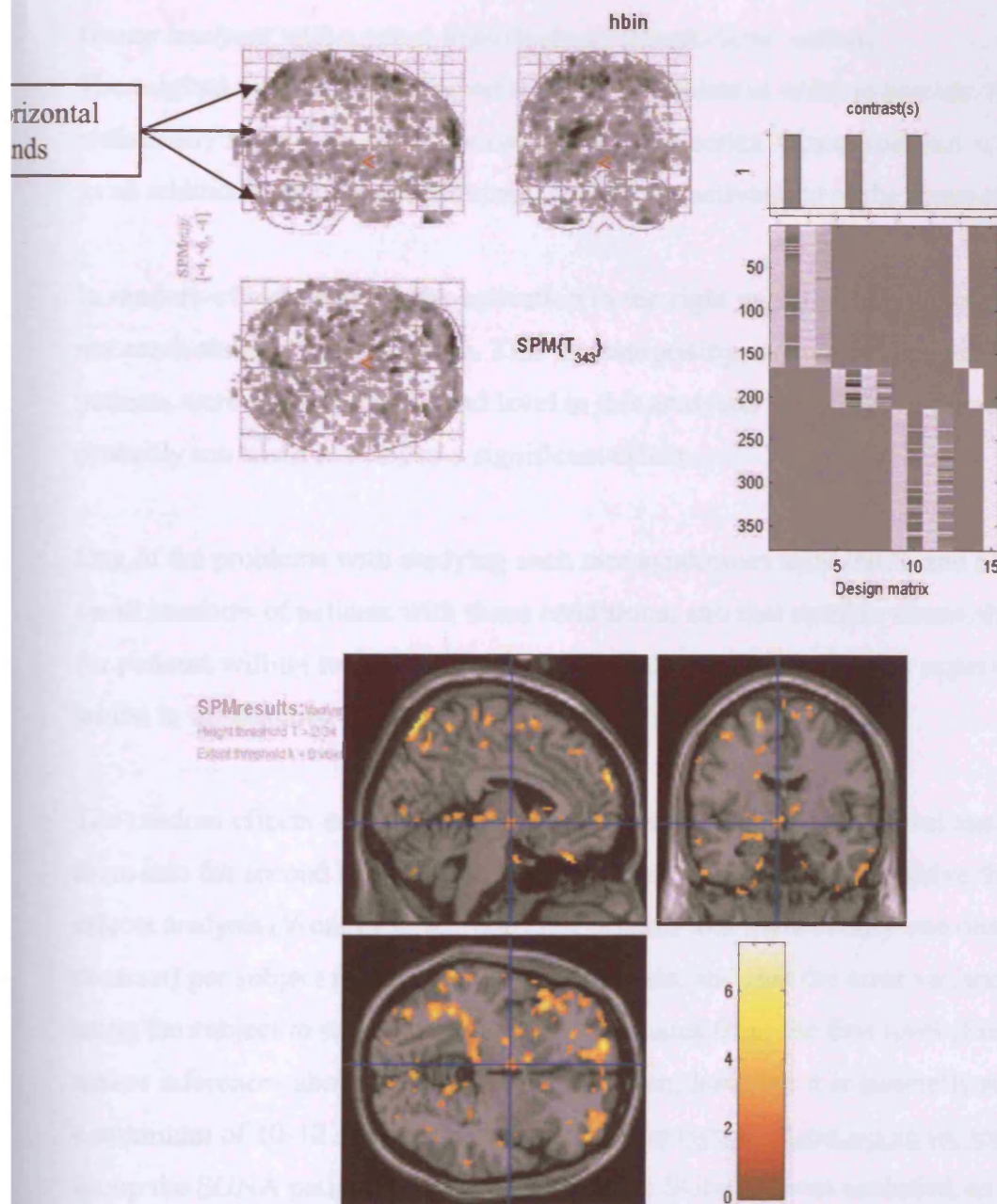
Most patients were taking preventive therapies up until 24 hours prior to the scans, and in most cases were having a good to moderate effect in suppressing the attacks. Therefore any scans performed under the influence of preventive medications would be influenced by the reduced frequency and severity of attacks. It is also plausible that some preventives may have a direct influence on hypothalamic activity, particularly melatonin (although none of our patients were taking it at this time). It has been noted that amitriptyline has an effect on the hypothalamic-pituitary axis (Barden et al., 1995), and it is possible that the lack of significant hypothalamic activation of Patient #2 may be due to his amitriptyline intake, although this effect has not been replicated in clinical studies (Rota et al., 2005).

In any case, all 8 patients who were taking preventives had stopped them 24 hours prior to the scan, and they were all experiencing attacks of SUNCT/SUNA, which would imply that the central generator of these attacks was not suppressed. PET studies in patients with PH and HC who stopped their medications 24-48 hours prior to scanning still demonstrated hypothalamic activation (Matharu et al., 2006b; Matharu et al., 2004c), and bilateral hypothalamic activation was still detected in a SUNCT patient who only omitted his medications on the day of the scan (Sprenger et al., 2005).

Movement related artefact

Two patients (#12, #17) were noted to have some head movement at the time of the scan. Both of their statistical parametric maps included horizontal 'bands' of activations which are characteristic of movement-related artefact (**Figure 13.1**). In the case of #12, the active voxels were not in the immediate region of interest, but in the case of #17 there was a band of active voxels in the plane of the region of interest. This may explain the reason why both patients had significant activation bilaterally, in both anterior and posterior regions. However the regions of interest were small in comparison to the total brain volume (10mm spheres), so it was decided to report them as active with this one caveat.

Figure 13.1
Horizontal bands as movement artefact in Patient #12



13. 9 Group analyses

Group analyses with a priori hypothesis of hypothalamic activity

The original analysis was done on individual patients in order to provide a stand-alone statistically significant result for each case in the series. Group analyses were performed as an additional step, to ascertain any significant activations of the group of patients.

In random-effects analysis the activation in the right posterior hypothalamic region did not reach statistical significance. This is unsurprising, as contrast images from only 9 patients were taken to the second level in this analysis; therefore the numbers were probably too small to achieve a significant effect.

One of the problems with studying such rare syndromes as SUNCT and SUNA is the small numbers of patients with these conditions, and that number diminishes even further for patients willing to take part in research trials, and those actually experiencing attacks whilst in the scanner.

The random effects analysis, which takes contrasts from the first level analysis and enters them into the second level analysis, is described as being more sensitive than the fixed-effects analysis (Worsley et al., 2002). It ensures that there is only one observation (i.e. contrast) per subject in the second-level analysis, and that the error variance is computed using the subject to subject variability of estimates from the first level (Friston, 2003). It makes inferences about differences in activation; however it is generally required to have a minimum of 10-12 subjects within each group (www.fil.ion.ucl.ac.uk/spm). In this group the SUNA patients and the symptomatic SUNCT were excluded, as these were thought to represent slightly different clinical phenotypes to idiopathic SUNCT. Therefore there were only 9 patients in the group analysis.

In the fixed-effects analysis, there was positive activation in regions of the anterior and posterior hypothalamus on both sides, with no significant negative activation.

A fixed-effects analysis estimates the error variance on a scan to scan basis, assuming that each scan represents an independent observation (Friston, 2003). It is likely to overestimate differences between patients (www.fil.ion.ucl.ac.uk/spm). Fixed effects analyses are used in the context of single case studies, or when the functional anatomy of interest replicates from subject to subject (Worsley et al., 2002). Inferences can only be made to the group of patients studied, and cannot be generalised to the population from which they were drawn (Friston et al., 1999).

It is used for the SUNCT patients; however the SUNA patients were excluded as they were thought possibly to have a different (negative) activation. The analysis was reported for only the binary pain states (attack on/off), and not for the headache parametrically analysed with pain rating. This was because the pain ratings were assigned as numbers (0, 1, 2, 3) relating to no attack, mild, moderate and severe pain. On an intra-individual level it makes sense to assess all 'mild' or 'moderate' attacks together; however there will be much inter-individual difference in rating the different severities of pain, such that one patient's 'moderate' may be different from that of the next patient. This inter-subject variability is borne out in functional imaging, where subjects with high sensitivity to pain activated the ACC significantly more than those who rated the same stimulus as less painful (Coghill et al., 2003). Therefore the fixed effects models was analysed only for the binary (attack on/off) states, and not for differential pain ratings.

The symptomatic SUNCT patient (#2) was excluded from both group studies due to no significant activation being found in the region of the hypothalamus for either binary or parametrically assessed attacks. This led to the assumption that patients with SUNCT or SUNA secondary to intracranial lesions may have a different pathophysiology to those with the idiopathic disease; and for this reason the patient was excluded from the group analysis.

Group analysis with no a priori hypothesis

All the original analyses had been performed under the hypothesis that there was activation in the region of the hypothalamus. The purpose of this analysis was to assess effects over the group of 9 SUNCT patients, assessing whole brain analysis with no correction for region of interest, to look for other areas activated during the attacks.

The areas activated were those in the 'pain matrix' (Ingvar, 1999), a term coined to represent the group of cortical and subcortical brain regions found to be commonly activated in studies of nociceptive stimulation. These include the primary and secondary somatosensory cortices (S1 and S2), insula, ACC, parietal cortex, dorsolateral prefrontal cortex (DLPFC) and the thalamus (Apkarian et al., 1999; Casey et al., 1996; Kwan et al., 2000; May et al., 1998b; Peyron et al., 2000; Talbot et al., 1991).

In this study there was activation in S1, insula, ACC and thalamus bilaterally. The thalamus was activated on both sides (Figure 12.26), although the local maximum of the cluster was on the right side. The activation of these structures thus confirm that the pain matrix is active in spontaneous attacks of pain as well as in experimentally induced painful states. In a case of spontaneous CH, there was activation ACC and medial thalamus based on small volume correction at the region of interest (Sprenger et al., 2004a), and the pain matrix was also active during spontaneous attacks of PH (Matharu et al., 2006b). There was also activation in the cerebellum, which has been documented in pain studies (Iadarola et al., 1998; Ploghaus et al., 1999). Activation in the bilateral frontal and insular region, parietal region and occipital cortex has been associated with cognitive evaluation of pain intensity (Kong et al., 2005), with signal change in S2 and insula increasing linearly with pain intensity (Bornhovd et al., 2002). The putamen and globus pallidus have been seen in capsaicin-induced pain, and are purported to be an initiation of withdrawal from the pain (Iadarola et al., 1998). Bilateral cerebellar activation associated with contralateral primary motor cortex activation has been reported (Coghill et al., 2001). The activation of subcortical structures such as the putamen, red nucleus and cerebellum which are mainly involved in motor function and reactive behaviour, is thought to be linked to pain avoidance and defence (Bingel et al., 2002).

Interestingly there was no activation in the region of the hypothalamus on this analysis. This may be because it used a different method to that of the *a priori* hypothesis. The previous method concentrated solely on the area of interest, and this method assessed the whole brain with a more stringent threshold ($P < 0.001$ for the whole brain, as opposed to $P < 0.01$ for the region-of-interest method). Therefore the hypothalamic activation may not have survived this threshold. This is discussed further in Chapter 18.

Alternatively it may be that there is no single locus of activation which is typical of all SUNCT patients within a fixed-effects analysis. In individual patient analyses, the results differed between patients, both in terms of psychophysical data (number and length of attacks) and in the functional imaging results. For instance, some patients had bilateral activation, and in some the activation was only unilateral, or even negative which was presumed to be a reciprocal deactivation to the activated side.

The laterality of the attacks should have been corrected by flipping all the scans so each patient's attacks seemed to be on the left side. However the patients with bilateral attacks or a propensity for bilateral attacks (#7, #23, #34) would not have fitted neatly into this category. Nevertheless, each patient in the group analysis had scans with attacks on the left side, and thus our original assumption that there is activation in the region of the contralateral hypothalamus should have manifested itself in this analysis.

13.10 Summary

It is therefore speculated that the activation seen in the region of the hypothalamus in individual patients remains specific to each individual, and that the common locus of activation in all patients with SUNCT is yet to be elucidated. It may not be as clear-cut as in groups of CH patients, where the ipsilateral posterior hypothalamus is demonstrated in both functional MRI (May et al., 1998a; May et al., 2000) and VBM (May et al., 1999a). The varying results observed between the patients may be because some patients have the potential for bilateral attacks, or that the hypothalamus is bilaterally active in some cases.

Patients with SUNA appear to have negative activation, and this may reflect the differences in phenotype between SUNCT and SUNA in terms of V_1 cranial autonomic symptoms.

The lack of hypothalamic activation on group assessment, using whole brain analysis and no *a priori* hypothesis, may be due to differences in statistical methods between the two types of analysis. Alternatively it may indicate the concept that the hypothalamus is not the only cause for SUNCT and SUNA, as will be discussed in Chapter 18.

Chapter 14

Voxel-Based Morphometry in SUNCT and SUNA

14.1 Introduction

A fundamental tenet of primary headache syndromes is that these disorders are due to abnormal brain function in the setting of normal brain structure. However this axiom has been called into question by the advent of voxel-based morphometry (VBM), an automated non-biased whole brain technique which analyses changes in brain structure (Ashburner and Friston, 2000). A VBM study in 27 CH patients showed a significant structural difference in grey matter corresponding to an increase in volume in the ipsilateral posterior hypothalamic grey, as compared to healthy controls (May et al., 1999a). In another study patients with chronic tension type headache were demonstrated to have a decrease in volume of structures associated with pain, such as the anterior and posterior cingulate cortices, insulae and the cerebellum (Schmidt-Wilcke et al., 2005). Interestingly there was no significant change in patients with migraine (Matharu et al., 2003b), or those with a history of migraine and analgesic overuse (Schmidt-Wilcke et al., 2005). It could therefore be speculated that there is a structural difference in posterior hypothalamic grey matter in TACs, but not in migraine.

This study aimed to assess 13 patients with SUNCT and SUNA using VBM, and to compare them to a group of 16 healthy controls. The *a priori* hypothesis was that there was a significant change in the volume of the grey matter in the region of the posterior hypothalamus, in patients with SUNCT and SUNA.

14.2 Methods- Voxel-Based Morphometry

Eleven patients (ten male) were recruited from our cohort of primary SUNCT, along with two patients with SUNA (one male). The patients' ages ranged from 33-72 years (mean 54.6 years). Sixteen healthy volunteers (12 male) were recruited as control subjects. They all gave no personal or family history of headache. Their ages ranged from 31-79 years (mean 55.4 years).

The study was approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee (REC Ref 97/033). The subjects gave their written consent for the study, and were free to withdraw from the study at any time.

Clinical Characteristics

Of the SUNCT patients, six had left-sided attacks. One patient (#23) had attacks affecting either side equally, and one (#7) had mainly left sided attacks but could occasionally get attacks on the right. Four patients had right-sided attacks. Of the SUNA patients, one had right-sided and one had left-sided attacks. One patient (#SUNA44) with left-sided attacks had another TAC on the right side, and one (#34) had a history of cluster headache and migraine (Empl et al., 2003). The clinical characteristics are displayed in Table 11.1.

14.3 Image Acquisition

MRI scanning was performed on a 1.5T magnetic resonance imaging (MRI) system (Siemens Vision). A high resolution (1 mm x 1 mm x 1 mm voxel size) T₁- weighted structural MRI was acquired for each subject.

Scanning parameters were as follows: TR (scan repetition time) = 12.24ms, TE (echo delay time)= 3.56ms, number of slices = 176, slice thickness of 1mm, giving voxels 1 mm x 1 mm x 1 mm. The same scanner parameters and scanner hardware were used for the acquisition of all anatomical volumes.

14.4 Image Processing and Spatial Normalisation

Structural images were preprocessed using VBM implemented with Statistical Parametric Mapping software (SPM5) (www.fil.ion.ucl.ac.uk/spm/), running under Matlab 6.5 (MathWorks, Natick, MA). Structural images were preprocessed in a single integrated segmentation and spatial normalisation routine. They were segmented to extract grey matter, and then normalised to an asymmetric T₁-weighted template in Montreal Neurological Institute (MNI) stereotactic space. During the normalisation a modulation

step was added to ensure that the total amount of gray matter in each voxel was conserved before and after spatial normalisation (after Good et al (Good et al., 2001a)). This involves multiplying the spatially normalised gray matter by its relative volume before and after spatial normalisation, and allows VBM to compare the absolute volume of grey matter structures, as opposed to comparing the relative concentration of these structures in non-modulated images. The images were then smoothed with a 12-mm FWHM (full width at half maximum) isotropic Gaussian kernel.

14.5 VBM Statistical analysis

A voxel-wise statistical analysis was performed on the modulated smoothed data using SPM5 (www.fil.ion.ucl.ac.uk/spm/), running under Matlab 6.5 (MathWorks, Natick, MA), employing the framework of the General Linear Model (Friston et al., 1995b). A second-level group analysis was performed, using multiple regressions with a constant. This models the average grey matter value over both the patient and the control groups.

A design matrix was constructed with three variables: group (patient = 1, control = 0), age, and laterality of attacks (right = 0, left = 1). The design matrix is shown in Figure 14.1.

Regionally specific differences in grey matter between the groups were assessed statistically using a two-tailed contrast, namely testing for voxel-wise increases or decreases in grey matter. Tests were applied using the following variables or combinations of variables:

- 1) group – i.e., differences between patients with SUNCT/SUNA as a group compared to controls
- 2) group and left sided attacks– i.e., differences between SUNCT/SUNA patients with left sided attacks as compared to controls
- 3) left sided attacks as a lone variable- i.e., differences between SUNCT/SUNA patients with left sided attacks compared to those with no left sided attacks and controls

- 4) group, left sided, and age- i.e., differences between SUNCT/SUNA patients with left sided attacks compared to controls, allowing for changes in age.

Contrast vectors for 'group' and 'group and left sided attacks' are shown in Figure 14.1 as an example.

Two voxel-wise parametric statistical methods were employed.

- a) Whole brain analysis, using corrections for the search volume, and implicit multiple comparisons, which were made for a family-wise error (FWE) P -value of 0.05. Activations were reported for each suprathreshold voxel at this level.
- b) Specific region of interest analysis, which did not involve correcting for the whole brain. This was specifically to evaluate the *a priori* hypothesis that there was a structural difference in the region of the posterior hypothalamus between patients with SUNCT/SUNA and healthy controls. The region of interest was selected as a 10mm sphere with its centre at the region of the posterior hypothalamus (x , y and z coordinates ± 6 , -16 , -6 mm from the anterior commissure respectively) and as a secondary test, the region of the anterior hypothalamus (x , y and z coordinates ± 6 , -6 , -6 mm respectively). Activations were reported for $P \leq 0.001$ at this threshold.

Both design matrices were repeated, with a reversal in the laterality; that is for the variable 'right sided attacks' right = 1 and left = 0. Logically speaking this was unnecessary, as the F -tests were two-tailed and would have detected either a positive or negative difference between left and right sides. However this was performed to account for Patient (#23) who had attacks on both sides, so his details were set as 1 in the laterality vector in both design matrices.

The entire study was repeated for patients with primary SUNCT only, and the SUNA patients were excluded from this analysis.

Figure 14.1
The Design Matrix for VBM

Figure 14.1a

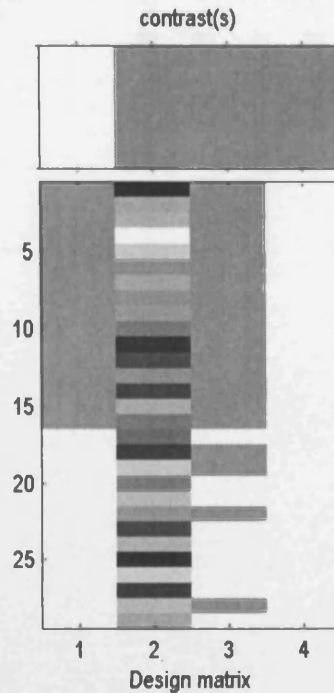
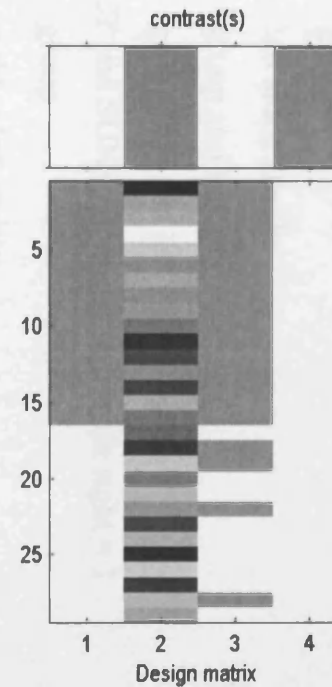


Figure 14.1b



The design matrix in VBM for all patients. Each horizontal line represents a patient's structural scan. Column 1 represents the group (controls = 0 (grey), patients = 1 (white)), Column 2 represents the age for each subjects, Column 3 represents laterality of symptoms (right = 0, left = 1), and the fourth column is the error term. Figure 14.1a looks at 'group' as the only contrast, with a contrast vector [1 0 0 0]. Figure 14.1b assesses the effect of group and left-sided attacks as contrasts, with contrast vector [1 0 1 0].

Chapter 15

Results: Voxel-Based Morphometry in SUNCT and SUNA

15.1 Whole Brain Corrected

With family-wise errors at a threshold of $P < 0.05$ corrected for whole brain, no suprathreshold voxels were found for the following contrasts:

- a) SUNCT and SUNA, design matrix with left = 1:
 - a. group
 - b. left sided attacks
 - c. group and left sided attacks
 - d. group, age and left sided attacks
- b) SUNCT and SUNA, design matrix with right = 1
 - a. group
 - b. right sided attacks
 - c. group and right sided attacks
 - d. group, age and right sided attacks
- c) SUNCT alone, design matrix with left = 1:
 - a. group
 - b. left sided attacks
 - c. group and left sided attacks
 - d. group, age and left sided attacks
- d) SUNCT alone, design matrix with right = 1
 - a. group
 - b. right sided attacks
 - c. group and right sided attacks
 - d. group, age and right sided attacks

15.2 Region of Interest Analysis

With the whole brain uncorrected for multiple comparisons, and at a threshold of $P < 0.05$, there were no voxels in the 10mm sphere in the region of the posterior hypothalamus (x, y and z coordinates $\pm 6, -16, -6$ mm), or the anterior hypothalamus (x, y and z coordinates $\pm 6, -6, -6$ mm) on either side, which survived significance to $P \leq 0.001$ uncorrected. These were performed for the following contrasts:

e) SUNCT and SUNA, design matrix with left = 1:

- a. group
- b. left sided attacks
- c. group and left sided attacks
- d. group, age and left sided attacks

f) SUNCT and SUNA, design matrix with right = 1

- a. group
- b. right sided attacks
- c. group and right sided attacks
- d. group, age and right sided attacks

g) SUNCT alone, design matrix with left = 1:

- a. group
- b. left sided attacks
- c. group and left sided attacks
- d. group, age and left sided attacks

h) SUNCT alone, design matrix with right = 1

- a. group
- b. right sided attacks
- c. group and right sided attacks
- d. group, age and right sided attacks

Chapter 16

Discussion: Voxel-Based Morphometry in SUNCT and SUNA

This study employed a sensitive, automated technique, VBM, to compare the brains of patients with SUNCT/SUNA with non-headache controls. The *a priori* hypothesis was that there is a change in the structure of the brain in the region of the posterior hypothalamic grey matter in patients with SUNCT and SUNA. This study revealed no such difference between patients and controls at the significance levels and thresholds set.

16.1 Methodology

Voxel-based morphometry is an unbiased automated whole-brain technique which can detect changes in the structure of grey or white matter which would go unnoticed in conventional structural imaging. Being an automated process and performing a statistical test at each voxel, it also reduces observer bias.

16.2 Field Strength of Scanner

The images were acquired on a 1.5 Tesla (1.5T) Siemens Scanner. It is possible that any structural differences between the two groups of patients were too subtle for this field strength of magnet, and that repeating the study on a 3T machine may yield positive results. However there have been positive results from studies performed in cluster headache operated on a 2T machine (May et al., 1999a), and in chronic tension type headache on a 1.5T machine (Schmidt-Wilcke et al., 2005). Still it may be useful to repeat this study using more powerful magnetic resonance imaging before declaring that there are absolutely no structural changes in SUNCT/SUNA.

16.3 Smoothing kernel

The smoothing kernel was set at 12mm FWHM, as has been described previously in VBM (Wright et al., 1995). Smoothing enhances the signal-to-noise ratio of the data and allows intersubject averaging by blurring differences in gyral anatomy between patients (Turner et al., 1998). The size of the smoothing kernel should reflect the size of the regional differences between the groups of brains (Ashburner and Friston, 2000). It has been noted using a previous version of SPM (SPM99) (www.fil.ion.ucl.ac.uk/spm) that using a smaller smoothing kernel in patients with schizophrenia elucidated hippocampal changes which were not seen on a larger smoothing kernel (Kubicki et al., 2002); however a review of more recent SPM software suggests that most studies should use a smoothing kernel of 12mm (Mechelli et al., 2005).

16.4 Inclusion and exclusion of patients

Patients with SUNCT and SUNA were included in one study, which was repeated with only SUNCT patients. There were no positive findings in either the combined group or the group of SUNCT patients alone. There would be an argument in favour of assessing purely SUNA patients; however it was felt that a group of only 2 patients would not yield significant results.

A patient with SUNCT secondary to a brainstem lesion (#2) was excluded from this study, due to the fact that his structural MRI showed an abnormal configuration of the deep grey matter at the lateral ventricles and the upper brainstem, and a lacune in the left thalamus. The grey matter abnormalities would be problematic in segmenting the images into grey and white matter with SPM, as well as difficulties with normalisation onto the standard Talairach space, so he was excluded from the study.

A patient with abnormal white matter lesions (#7) was included in the study for two reasons. First, the lesions were entirely in the white matter, and would therefore not be included in the analysis which assessed purely segmented grey matter. Secondly, this

patient was thought to have primary (idiopathic) SUNCT, and these lesions were not considered to be the cause of his headaches.

16.5 SUNCT and SUNA

This study included both SUNCT and SUNA patients as one group. However there are differences noted between these two conditions in terms of phenotype (Chapter 6), their responses to treatment (Chapter 10), and also in functional imaging (Chapter 13); the latter of which showed activation during attacks of SUNCT and deactivation during SUNA attacks. Both SUNCT and SUNA were included in one VBM design matrix, as it was thought that any abnormal activation *per se*, be it positive or negative, would be associated with a structural change in the region of the hypothalamus. There were no positive findings in this analysis. Even taking primary SUNCT alone as an isolated syndrome, there were no suprathreshold voxels found.

16.6 Number of patients

Only 13 patients and 16 healthy controls were included in this study. Some VBM studies have used much larger groups, such as a seminal study of ageing in 465 people (Good et al., 2001a). The VBM study in CH assessed 25 patients and 29 controls (May et al., 1999a), and another study compared 20 patients with chronic tension-type headache and 20 patients with medication-overuse headache with 40 controls (Schmidt-Wilcke et al., 2005). The SUNCT and SUNA group was smaller than this, and may be a reason why no statistically significant result was found. However the small number of patients cannot be the only reason for negative results in this group, as there have been positive findings recently in small groups of 9 and 13 children with high-functioning autism and Asperger's syndrome respectively, compared to a group of 13 controls (Kwon et al., 2004).

16.7 Modulation versus non-modulation

In standard normalisation, individual images are warped to match a template, and thus volumetric differences are likely to be introduced. For example, if the subject's hypothalamus is smaller than that of the template, then it would be warped on to a larger size, voxel-for-voxel, and the information of this region would be lost. In this case, VBM compares the relative *concentration* of the structures in the spatially normalized regions. However this study sought to assess the relative *volume* of the hypothalamus; therefore a modulating step was added in at the normalisation level to compensate for the effect of spatial normalization. Analyses on modulated data appear to be more sensitive to regionally specific macroscopic change than analyses on unmodulated data (Good et al., 2001b). It is possible that any change in the hypothalamus may have been a concentration-related change, and not a volume-related change. However the process of modulation has been employed in two positive studies which documented differences in the hypothalamus in cluster headache (May et al., 1999a) and in pain-producing structures in chronic tension type headache (Schmidt-Wilcke et al., 2005).

16.8 Laterality

Some patients had unilateral attacks, and some had bilateral attacks; similarly on functional imaging the activation was ipsilateral, contralateral or bilateral. Therefore the inclusion of laterality of attacks as a variable for the VBM analysis may have produced meaningless results. However even on using the variable 'group' alone, there were no significant differences seen between the patient and the control group.

16.9 A Negative Result

Given all of these shortcomings in the methodology, it may still be possible that there is no structural difference at a voxel-based level between patients with SUNCT/SUNA and healthy controls.

It has been fundamental to the concept of primary headache syndromes that they were associated with abnormalities in neuronal function (as assessed on functional imaging) with completely normal brain structure (May et al., 1999a). The development of VBM as a technique has allowed exploration of structural changes in syndromes such as cluster headache (May et al., 1999a), schizophrenia (Wright et al., 1995), and indeed in normal ageing (Good et al., 2001a), which would be undetected on conventional MRI. However this study found no structural changes in SUNCT or SUNA.

It is interesting to note that no structural changes were found on VBM in migraine (Matharu et al., 2003b). Given the genetic basis for migraine (De Fusco et al., 2003; Dichgans et al., 2005; Haan et al., 2005; Ophoff et al., 1997; Ophoff et al., 1996; Terwindt et al., 1998), and the spectroscopic studies showing abnormal energy metabolism in the brains of patients with migraine (Montagna, 1995; Montagna et al., 1994; Sandor et al., 2005b), one might expect a structural change in migraineurs on voxel-based morphometry. However the negative findings in VBM may be explained by the fact that this study assessed regional changes between migraine patients and controls; a mitochondriopathy or other genetic abnormality would encompass the whole brain, and indeed other tissues such as skeletal muscle (Lodi et al., 1997). A migraine attack may be generated or mediated by the brainstem and dorsal rostral pons in an already metabolically hypofunctioning system, but this may not necessarily require a structural change in these areas at a voxel-based level. The rationale that regional functional abnormalities can exist without structural changes can be extrapolated to SUNCT and SUNA.

A negative result in SUNCT/SUNA would conflict with the findings in cluster headache, which is the only other TAC to be studied with VBM (May et al., 1999a). Reasons for this may include differences between CH and SUNCT/SUNA in terms of manifestation of phenotypic features related to the hypothalamus. For example, CH has a strong diurnal variation, with 'clock-like' regularity, and a nocturnal propensity of attacks in around 75% of patients (Russell, 1981). In contrast, only 7% of SUNCT and no SUNA patients reported attacks mainly occurring at night (Chapter 5.11). Secondly, patients with CH

respond to melatonin (Leone et al., 1996; Peres and Rozen, 2001), whereas it has been rather disappointing in the few SUNCT/SUNA patients who have tried it (Chapter 10.5.8). Lithium is also used to good effect in CH (Bussone et al., 1990; Ekbom, 1981; Peres and Rozen, 2001; Steiner et al., 1997b), and it is assumed to act by accumulating in the hypothalamus (Dodick et al., 2003) and enhancing serotonergic transmission in the central nervous system (Price et al., 1989). It has been tried in a limited number of our patients without success (Chapter 7.5.11), suggesting that hypothalamic manipulation may not be the effective target for therapy in these syndromes. Other differences include the ability to trigger SUNCT/SUNA through cutaneous stimuli, which is not the case in CH, and of course the difference in attack length (15-180 minutes in CH versus 5-240 seconds in SUNCT) (Headache Classification Committee of The International Headache Society, 2004). Finally, the positive findings in cluster headache in one paper (May et al., 1999a) have not yet been reproduced, so there is the possibility that it may not represent a sustainable theory of structural differences in primary headache syndromes.

It is therefore possible that although CH and SUNCT share some aspects of their phenotypes, and they both have activation in the posterior hypothalamic region in functional imaging studies, and also both respond to deep brain stimulation at the posterior hypothalamus (Franzini et al., 2003; Leone et al., 2003b; Leone et al., 2004a; Leone, 2004); the pathophysiology of these syndromes is different, and may be manifest by a structural change in the hypothalamus in CH, with no such change in SUNCT/SUNA.

PART IV. DISCUSSION

Chapter 17

Symptomatic (secondary) SUNCT and SUNA

Primary SUNCT and SUNA, like other primary headache syndromes, are defined as being not attributable to another cause (Headache Classification Committee of The International Headache Society, 2004). However it is recognised that if a new headache occurs for the first time in close temporal proximity to another disorder that is a known cause of headache (such as an intracranial vascular event, infection and so on), then it is classified according to the precipitating disorder, even if it has the characteristics of a primary headache syndrome such as migraine, CH or any of the TACs (Headache Classification Committee of The International Headache Society, 2004).

The concept of post-traumatic headache requires that the headache syndrome starts within seven days of sustaining the trauma (Headache Classification Committee of The International Headache Society, 2004). In this series there are two patients (#42 and #52) with onset of SUNCT within one week of trauma. For other SUNCT patients the trauma is less acute, (Chapter 5.15 and Table 5.14), although occurring within weeks in each case. However it may remain that these headache syndromes were precipitated as a result of the trauma sustained.

Chronic headache following trauma to the head or neck is well described, with the duration of headache being independent of the type or severity of trauma (Warner, 2000). In terms of other TACs, there exist post-traumatic forms of CH (Reik, 1987; Turkewitz et al., 1992) and PH (Irimia et al., 2005; Matharu and Goadsby, 2001). A syndrome resembling SUNCT was described after a head injury, but it was diagnosed as TN because of a sensory deficit in V_1 (Putzki et al., 2005). However abnormal sensory examination is described in 12% of the current SUNCT series, so this may not be a reason for dismissing the diagnosis of SUNCT.

A review of PH, HC and SUNCT in association with other pathologies has led to the suggestion of criteria to be considered in symptomatic headache syndromes, including close relationship in time and side of the lesion, remission on treatment of the lesion, and long-term follow-up (Trucco et al., 2004). It has been argued that local lesions in the cavernous sinus can cause syndromes resembling CH (Koenigsberg et al., 1994) and PH (Irimia et al., 2005), and that local lesions such as intraorbital metastatic bronchial carcinoid can cause SUNCT (Black et al., 2005). One could reason that the local lesions cause an ipsilateral syndrome of pain and autonomic symptoms; that the pituitary lesions could cause SUNCT via the hypothalamic-pituitary axis, and that the posterior fossa and brainstem lesions have a local action either on the trigeminal nerve root, or at the trigemino-cervical complex, or on the ascending pathways. However, there are SUNCT patients with intracranial lesions that anatomically may not account for the pain; Patients #57 and #51 who had parietal or parieto-occipital lesions, and Patient #7 with generalised cerebral white matter lesions, who had bilateral hypothalamic activation on fMRI. It is unclear as to whether these lesions were a direct cause of the SUNCT attacks, or whether they are incidental findings unassociated with the headache symptoms. Indeed in both patients #57 and #51, the pain persisted after excision of the lesions.

Classifying primary headache syndromes according to their clinical phenotype and secondary headaches according to the underlying cause is well-recognised, although there exist secondary headache syndromes which have the same clinical phenotype as the primary syndrome. Examples of these are SUNCT secondary to prolactinoma (Levy et al., 2003; Matharu et al., 2003c), and migraine caused by an angioma in the brainstem (Afridi and Goadsby, 2003) or migraine-like attacks after stereotactic intervention to the periaqueductal grey matter (Raskin et al., 1987; Veloso et al., 1998). The genetics of migraine are starting to be documented (De Fusco et al., 2003; Dichgans et al., 2005; Haan et al., 2005; Ophoff et al., 1997; Ophoff et al., 1996; Terwindt et al., 1998), so in patients with no previous history or family history of migraine it would be tempting to speculate that these migraine-like attacks resulted directly from the lesion or intervention. However the genetics of CH (Haan et al., 2005; Ophoff et al., 1997; Ophoff et al., 1996;

Terwindt et al., 1998), PH (Cohen et al., 2006) and SUNCT (Gantenbein and Goadsby, 2005) are much less well-defined, so it is unclear as to whether the patients with supposed symptomatic SUNCT/SUNA secondary to intracranial lesions were predisposed to develop these syndromes, and the lesion was either incidental or by some mass effect or shearing force precipitated the start of the attacks; or whether indeed the lesion was the only cause of the headache syndrome.

Table 17.1 shows the patients with SUNCT/SUNA and intracranial lesions, and shows their responses to various medications. It is noted that in all SUNCT and SUNA patients, indomethacin had no effect and intravenous lidocaine had a beneficial effect (table 7.4), and in secondary SUNCT/SUNA this is no different. Oxygen generally has no effect in SUNCT/SUNA, although in one patient (#57) it changed the quality of her pain from a sharp to a burning type pain. In terms of preventives, 3 of the 4 SUNCT and the SUNA patient had a moderate to good effect on lamotrigine, and 3 of 7 SUNCT patients had some benefit on gabapentin, which reflects the figures for the total group of primary and symptomatic SUNCT/SUNA combined. However only one of the 4 SUNCT patients had a moderate benefit with topiramate, and only one in 6 had success on carbamazepine, which is less than that observed in the total group. It would therefore stand to reason that the lack of response to indomethacin and the good response to intravenous lidocaine would aid in the diagnosis of SUNCT or SUNA, either in its primary form or secondary to intracranial lesions. Intravenous lidocaine may also be useful to provide some respite from the pain for up to weeks or months at a time. In terms of preventives, lamotrigine appears to be useful both in primary and secondary SUNCT/SUNA.

In terms of treating the primary cause, two patients with pituitary lesions (#20 and #37) had treatment of the primary lesions, with good effect in resolution of the headaches in one patient (#37), and with some residual SUNCT attacks in the second patient. In both patients with space occupying lesions (#51 and #57) the attacks persisted after the lesions were removed.

Table 17.1

Secondary SUNCT/SUNA and their responses to medications

SUNCT							
Patient number	Oxygen	Indotest	iv lidocaine	Lamotrigine	Topiramate	Carbamazepine	Gabapentin
Vascular loops							
46	no effect (low flow)	-	-	-	-	no effect	minimal
13	minimal	negative	-	good in combination	no effect	good in combination	no effect
55	-	negative	-	-	moderate	no effect	no effect
White matter changes							
52	-	negative	-	moderate	-	no effect	good
7	no effect	-	pain free 3 weeks	moderate	minimal	no effect	moderate
Pituitary lesions							
20	-	-	-	-	-	-	-
25	-	-	-	good	-	-	moderate
37	-	-	-	-	-	-	-
Space occupying lesions							
51	-	-	-	-	-	-	-
57	changed type of pain	negative	reduced frequency & duration	no effect	no effect	no effect	no effect
SUNA							
Patient number	Oxygen	Indotest	iv lidocaine	Lamotrigine	Topiramate	Carbamazepine	Gabapentin
White matter changes							
SUNA4	-	-	-	Good	-	-	-

The presence of an intracranial lesion may cause a mass effect, or a head injury may cause axonal injury and shearing effects, which are well documented after direct mild to moderate head injury, and physiological changes have been noted after concussion injuries (Saper, 2000). It is therefore plausible to speculate that, just as the dorsal raphe nucleus may sustain a physiological abnormality post-traumatically, and lead to chronic migraine (Raskin et al., 1987), there may be a physiological shift in the hypothalamus following trauma which may lead to the development of SUNCT or SUNA.

The functional imaging study found activation in the posterior hypothalamic region bilaterally in Patient #7 with generalised white matter lesions, but no significant activation in Patient #2 who developed SUNCT after an episode of ataxia, and who had an unusual configuration of the brainstem and a lacune in the thalamus. It is suggested that Patient #7 had primary SUNCT with incidental white matter lesions which are anatomically remote, and that Patient #2 had symptomatic SUNCT, secondary to his brainstem lesion. It would be very interesting to image patients with SUNCT secondary to other causes, particularly those with neurovascular compression of the trigeminal loop, in whom one might expect no hypothalamic activation if the syndrome was purely due to the local compression, but one would see hypothalamic activation if the syndrome was centrally generated or modulated.

Two problems arise with functional imaging in patients with intracranial lesions; the first is that some post-surgical patients will be unable to enter the MRI scanner if there are metal clips or stitches *in situ*; and secondly that the residual neuroanatomy may be so abnormal (after resection of a large tumour, or due to an abnormal configuration as in Patient #2), that the normalisation of the patient's scans onto standard Talairach space may involve greater warping than for normal brains, with resultant loss of anatomical integrity or distortion of the location of the BOLD signal.

Chapter 18

SUNCT, SUNA, TACs and the hypothalamus

18.1 Neuromodulation and a central generator for TACs

It has been argued in Chapter 10.7 that greater occipital nerve injections can modulate the behaviour of the trigeminal nociceptive complex in order to provide relief from the pain. Suboccipital electrical stimulators have had some useful effect in HC and CH (Dodick et al., 2003), although this effect was not replicated in a recent group of 5 patients with CCH (Schwedt et al., 2006). This was probably due to the short followup time (3-6 months), during which time the stimulation parameters may not have been optimised, and also due to the fact that the stimulators were only implanted on the ipsilateral side and not bilaterally.

Occipital nerve stimulation may also cause a modulation of central pain-producing structures, such as the dorsal rostral pons, anterior cingulate cortex and cuneus, as seen in PET when turning off bilateral occipital nerve stimulators in chronic migraine (Matharu et al., 2004a).

Surgery to the trigeminal nerve, such as local nerve blockades, stellate ganglion block, supraorbital nerve block, and invasive surgery such as microvascular decompression of the trigeminal nerve, glycerol rhizotomy and γ knife radiosurgery, have had variable or no beneficial effect in SUNCT, as discussed in Section 10.6. This is in contrast with TN, which has a good response rate to microvascular decompression (Barker et al., 1996). It has also been shown in this cohort that one SUNCT patient had a supraorbital nerve injection and one had an infraorbital nerve injection which caused numbness but the attacks were still triggerable. This would concur with persistence or recurrence of CH attacks after trigeminal root section (Leone et al., 2004a; Matharu and Goadsby, 2002a),

in 10/17 patients undergoing trigeminal gangliorhizolysis (Mathew and Hurt, 1988), and in 8/10 patients undergoing γ knife radiosurgery (Donnet et al., 2005).

There is however one case of SUNCT with bilateral hypothalamic activation on functional imaging and a blood vessel compressing the ipsilateral trigeminal nerve, with resolution of the attacks after decompressive surgery (Sprenger et al., 2005). However the followup time was only 7 months, and as the patient had a remission of 10 months in the previous year, this could just have been a remission period and not a true reflection of the outcome of the procedure.

These, along with extensive functional imaging studies in CH, other TACs and HC, provide strong evidence that these headache syndromes are centrally generated. The cranial autonomic symptoms are also believed to be centrally driven, as evidenced by HC and CH patients who had achieved analgesia with occipital nerve stimulation, who retained some autonomic features (Schwedt et al., 2006). One of the SUNCT patients (#57) could have autonomic features without the attacks, and one SUNA patient (#SUNA44) had cessation of the painful attacks on intravenous lidocaine, but with continuation of the autonomic symptoms. This would suggest that even though the peripheral pain had been blocked or was absent, there is still a central generator for the attacks, likely the hypothalamus, mediating these effects via the hypothalamic-autonomic reflex (May and Goadsby, 1999), and that the cranial autonomic symptoms are not just a manifestation of the trigeminal-autonomic reflex. This putative difference in the origin of the autonomic symptoms may explain the difference between SUNCT and trigeminal neuralgia with lacrimation (Goadsby et al., 2001).

18.2 Hypothalamic activation on functional imaging

The activation of the hypothalamus in all TACs has come from functional imaging studies in CH (May et al., 1998a; May et al., 2000), PH (Matharu et al., 2006b) and SUNCT (Cohen et al., 2004a; May et al., 1999b; Sprenger et al., 2005). Deep brain hypothalamic stimulation has had a good effect in a series of 16 CH patients (Franzini et

al., 2003; Leone et al., 2004b), and in a single case of SUNCT(Leone et al., 2004b); thus adding further evidence for the role of the hypothalamus in these syndromes. The current study adds to the evidence that there is activation in the area of the hypothalamus in SUNCT/SUNA, although with a few caveats:

- 1) the study set out with an *a priori* hypothesis that there is hypothalamic activation in attacks of SUNCT and SUNA. The *a priori* hypothesis is met on assessing the region of interest in individual cases and on group analysis, yet on whole brain analysis in the group with no *a priori* hypothesis there is activation of the pain matrix but no activation in the hypothalamic region
- 2) methodological issues in this study vary from other studies and so the results may be interpreted differently
- 3) the activation shown in this study is less uniform than that seen in other syndromes; activation is
 - a. ipsilateral in CH (May et al., 1998a; May et al., 2000)
 - b. contralateral in indomethacin-sensitive headaches (Matharu et al., 2006b; Matharu et al., 2004c)
 - c. and may be bilateral in SUNCT (Cohen et al., 2004a; Sprenger et al., 2005)

In this study the activation is posterior or anterior, and there can be ipsilateral, contralateral or bilateral activation; thus calling into question the ability to generalise across the population of SUNCT and SUNA patients.

This serves as further evidence to link the TACs as a supergroup of headaches, but to separate them according to their clinical and therapeutic differences. Further differences between the individual TACs may be borne out by the discrepancies in laterality of activation.

18.3 Location of the hypothalamus

The location of the hypothalamus is also an issue. In functional imaging the area activated is the posterior hypothalamus, as is the area used in deep brain stimulation. This area is anatomically distinct from the suprachiasmatic nucleus which controls circadian

rhythms. In this functional imaging study, both the anterior and the posterior areas of the hypothalamus were assessed, and activation in the anterior aspect of the hypothalamus has been reported in previous studies of SUNCT (Cohen et al., 2004a; Sprenger et al., 2004b; Sprenger et al., 2005), which may contradict the findings that posterior hypothalamic deep brain stimulation is successful in SUNCT (Leone et al., 2005).

The current functional imaging study assessed a region of interest with its centre as the coordinates cited in previous functional imaging studies. It can be seen in certain patients (for example #56 and #SUNA40) that although the *T* test showed a statistically significant result, the centre of the cluster of activation was not actually at the hypothalamus. We have reported these as positive activations as they would refute the null hypothesis that there was no activation in the region of the posterior hypothalamus, as specified by this region of interest. However it is possible that this region of interest may encompass areas outside those which would physiologically function as the hypothalamus.

Furthermore, PH which is another TAC, and hemicrania continua which is not a TAC but shares some characteristics, both have activation in the posterior hypothalamus and also the ventral midbrain (Matharu et al., 2006b; Matharu et al., 2004c). As both of these syndromes respond absolutely to indomethacin, it is tempting to speculate that indomethacin may have an action at the ventral midbrain.

However the weakness of functional imaging techniques is that they provide regions of significant change on brain volumes without directional information about the ascending or descending nociceptive inputs from which these changes result (Jones et al., 2003). Hypothalamic activation has been reported in previous studies of experimental pain (Hsieh et al., 1996a), as well as in other pain studies (Ingvar, 1999; Jones et al., 2003; Kupers et al., 2000; Sanchez del Rio and Alvarez Linera, 2004). There is evidence that the hypothalamus is involved in nociception (Bartsch et al., 2004). The functional imaging results can therefore only be interpreted with reference to clinical, anatomical, biochemical, electrophysiological and pharmacological results derived from animal and

human studies. With the currently available data, it remains inconclusive whether the posterior hypothalamic activation is the central generator of the attacks, of whether it is active in an anti-nociceptive role secondary to the pain, or whether it is part of a cascade which originates higher in the brain.

Deep brain stimulation in the posterior hypothalamic region has had a good effect in suppressing attacks of CH and SUNCT. Therefore it may be a good therapeutic target for the future in TACs, even if the hypothalamus is not the primary generator of the attacks.

18.4 Non- imaging evidence for hypothalamic involvement

Evidence for hypothalamic involvement also stems from the fact that SUNCT/SUNA are TACs and related to CH. For example, the hypothalamus is known to regulate circadian (and seasonal) rhythms, which are a striking feature of CH, with nocturnal attacks occurring in 75% of cases (Russell, 1981), and episodic CH occurring in seasonal bouts (Bahra et al., 2002), with highest bout frequency at the summer and winter solstices, apparently related to the length of daylight (Kudrow, 1987). These features are present in SUNCT but to a much smaller degree, and in fact 89% of SUNCT patients had the primary chronic form without seasonal bouts (Table 5.13), and only 7% of SUNCT patients had predominantly nocturnal attacks (Table 5.11).

The biochemical studies which demonstrated abnormal levels of serum testosterone, cortisol, prolactin, melatonin, and thyroptropin in CH patients, suggesting hypothalamic dysfunction (Leone and Bussone, 1993) have not been done in SUNCT/SUNA. There is one case report of SUNCT with a low serum testosterone whose attacks were reduced on treatment with clomiphene citrate which increases testosterone levels directly via the hypothalamus, but which then relapsed at the seasonal ‘change of the clocks’ (Rozen et al., 2005).

The apparent discrepancies between CH and SUNCT/SUNA may also be reflected in their responses to medications; for instance oxygen an acute abortive therapy in CH has

been suggested to act either on abnormal mitochondrial energy metabolism (as suggested in Chapter 2.8), or in nocturnal CH attacks which are possibly due to hypoxia in an already physiologically compromised hypothalamus (Cohen and Kaube, 2005; Kudrow, 1983; Nobre et al., 2003).

That the hypothalamus is a generator of CH attacks is further evidenced by the beneficial action of melatonin (Leone et al., 1996; Peres and Rozen, 2001), and the fact that melatonin production is reduced in CH patients, both nocturnal release and when measured over a 24-hour period (Chazot et al., 1984; Leone and Bussone, 1993; Leone et al., 1995; Waldenlind et al., 1987) and circannual melatonin (Waldenlind et al., 1994). Melatonin therapy is presumed to act in cluster headache by supplementing the reduced melatonin secretion by a malfunctioning pineal system, and has been linked to the diurnal hypothalamic rhythm found in CH, by preventing both the nocturnal and daytime attacks (Peres and Rozen, 2001). However it is also reported to be beneficial in open-label trials in other headache syndromes such as migraine and hemicrania continua, and has been suggested to have many mechanisms of action, such as an anti-inflammatory effect, free radical scavenging, and membrane stabilisation (Peres, 2005). Melatonin treatment has had a limited effect in SUNA patients (albeit in small numbers), possibly because SUNA patients are more refractory to treatment than SUNCT patients. Alternatively the pathophysiology between SUNCT and SUNA, in terms of hypothalamic involvement, may be different, and that in itself may be different from the hypothalamic activation in CH.

One of the effective preventive treatments for CH is lithium (Bussone et al., 1990; Ekbom, 1981; Peres and Rozen, 2001; Steiner et al., 1997b). Lithium accumulates in the hypothalamus (Dodick et al., 2003), and acts by increasing the absorption of tryptophan and promoting its transformation to 5-HT, thus enhancing serotonergic neurotransmission in the central nervous system (Price et al., 1989). The hypothalamic pacemaker is innervated by 5-HT, and lithium possibly exerts its effects on the circadian rhythms by slowing and altering them via this mechanism (Kafka et al., 1982; Kripke and Wyborney, 1980). Lithium has been shown to decrease REM sleep in both healthy and depressed

people (Billiard, 1987). Moreover, both tryptophan and 5-HT are precursors for melatonin synthesis, and lithium has been shown to increase nocturnal melatonin levels in patients with CH (Chazot et al., 1987). However lithium has had no effect in the three SUNCT/SUNA patients who tried it (Table 7.7). Again this may be due to the small numbers of patients, or it may be that the pathophysiology of SUNCT and SUNA is different to that of CH in terms of hypothalamic activation, and thus they have different responses to treatment with lithium.

18.5 The role of the hypothalamus in TACs, SUNCT and SUNA

It is interesting to observe that the clinical feature that is common to the four primary headache syndromes in which posterior hypothalamic activation has been reported (i.e. PH, CH, SUNCT and HC) is prominent cranial autonomic features in association with the headache. It has been suggested that the pathophysiology of these syndromes revolves around the trigeminal-autonomic reflex (Goadsby and Lipton, 1997). There is considerable experimental animal literature to document that stimulation of trigeminal efferents can result in cranial autonomic outflow, the trigeminal-autonomic reflex (May and Goadsby, 1999). In fact, some degree of cranial autonomic symptomatology is a normal physiologic response to cranial nociceptive input (Frese et al., 2003; May et al., 2001) and patients with other headache syndromes, such as migraine, may report these symptoms (Barbanti et al., 2002; Benoliel and Sharav, 1998). It has been suggested that the cranial autonomic symptoms may be prominent in these syndromes due to a central disinhibition of the trigeminal-autonomic reflex by the hypothalamus (Benjamin et al., 2004). Indeed, there are direct hypothalamic-trigeminal connections (Malick and Burstein, 1998), and the hypothalamus is known to have a modulatory role on the nociceptive and autonomic pathways, specifically trigeminovascular nociceptive pathways (Bartsch et al., 2004).

The current classification of primary headache syndromes in general, and TACs in particular, is based largely on clinical phenotype, with response to indomethacin in PH and HC (Headache Classification Committee of The International Headache Society,

2004). It is possible that HC and PH have a different pathophysiology to CH and SUNCT, which is why they respond to indomethacin and CH and SUNCT do not. The hypothalamus is suggested to be the mediator of the attacks in TACs on clinical grounds largely due to evidence gathered from CH, such as biochemical abnormalities and the diurnal and seasonal variations in CH (Cohen and Kaube, 2005). The act of including PH and SUNCT/SUNA as TACs from a phenotypic basis stems from the fact that they are all unilateral, relatively short-lasting attacks of severe orbital, retro-orbital or temporal pain, with ipsilateral cranial autonomic symptoms (Headache Classification Committee of The International Headache Society, 2004). The agitation and restlessness stated in CH has also been shown in this series of SUNCT patients. The differences between the syndromes lie not only in the duration and frequency of the attacks, but also in their response to medications, such that CH responds well to oxygen (Fogan, 1985; Kudrow, 1981) and sumatriptan (Diener, 2001; Ekbom et al., 1993; Hardebo, 1993); PH to indomethacin (Antonaci et al., 1998); and SUNCT/SUNA to intravenous lidocaine as shown in this series. Other differences include the ability to trigger SUNCT/SUNA attacks by cutaneous stimuli, which is generally not the case in other TACs.

It has been suggested in CH that although there is clear evidence that the attacks are centrally generated and that hypothalamic activity is key to the attacks, this activity may not generate an attack directly, but that an abnormality in hypothalamic function facilitates a cascade of metabolic and biochemical events, including deranged melatonin, cortisol and 5-HT metabolism, which in turn would trigger an attack (Cohen and Kaube, 2005). It is also possible in SUNCT and SUNA that the hypothalamus plays a role either as a generator or modulator of the attacks, but indirectly via mechanisms yet to be elucidated, and there may be other mechanisms for the pathophysiology of these syndromes that are yet unknown. This may explain the differences between SUNCT and other TACs in terms of the functional imaging results, phenotype and response to medications.

Chapter 19

SUNCT and SUNA- a spectrum

SUNCT and SUNA can be thought of as different manifestations within a spectrum of a disorder, as they share many of the same characteristics of unilateral, episodic severe pain that occurs in stabs or jabs and is associated with ipsilateral cranial autonomic outflow. Both may be associated with cutaneous triggering of attacks, there is a lack of refractory period in both syndromes, and both respond to intravenous lidocaine and not to indomethacin. However there is an argument for separating out the two syndromes; and thus there are differences between them that are not simply the presence of Conjunctival Injection and Tearing that would make a diagnosis of SUNCT as opposed to SUNA.

The differences in this series of 52 patients (43 SUNCT and 9 SUNA) are as follows:

- 1) SUNCT affects mainly men, and SUNA affects mainly women
- 2) SUNCT is more likely to affect the orbital and supraorbital regions, and SUNA is more likely to affect the temple, V₂ and V₃
- 3) In terms of triggering of attacks, most SUNCT patients had mainly triggered attacks, whereas most SUNA patients had mainly spontaneous attacks (Table 5.12)
- 4) Patients with SUNCT were more likely to respond to medications such as lamotrigine, topiramate and melatonin, and to procedures such as the GON injection (Table 7.7)
- 5) In fMRI, SUNCT patients had positive activation in the region of the posterior or anterior hypothalamus, either contralaterally or bilaterally, or negative activation on the ipsilateral side. Both SUNA patients had negative activation only

These may simply be a consequence of small group sizes, especially with only 9 SUNA patients in the clinical study and 2 in the functional imaging study, and these findings may not be significant enough to comment. However the question is asked: Is SUNA

more refractory to treatment than SUNCT? And is this an effect of lack of conjunctival injection and tearing?

The presence of autonomic symptoms in V_1 , which are conjunctival injection and lacrimation, in SUNCT may be due to the trigeminal autonomic reflex (May and Goadsby, 1999), as pain in other headache syndromes can give rise to autonomic symptoms (Barbanti et al., 2002; Benoliel and Sharav, 1998), although generally to a lesser degree than that seen in TACs (Goadsby et al., 2001). Indeed, one patient (#59) specifically reported lacrimation when his pain was predominantly in V_2 and nasal congestion when his pain was predominantly in V_3 , thus suggesting a topographical arrangement in the trigeminal-autonomic reflex. It is known from functional imaging work that the trigeminal nucleus shows somatotopic activation in pain according to the three divisions of the trigeminal nerve (DaSilva et al., 2002). As most of the SUNA patients in this series had V_2 and V_3 pain, it is plausible to suggest that this could explain their lack of V_1 autonomic symptoms in the eye.

The concept of cutaneous triggering is specific in SUNCT and SUNA as compared to the other TACs, although factors such as alcohol and strong smells such as paints and solvents, can trigger CH (Bahra et al., 2002) and PH (Cohen et al., 2006). There is a relative discrepancy between the two syndromes, in that most of the SUNCT patients had triggered attacks, and most of the SUNA patients had mostly spontaneous attacks. This may in turn affect their autonomic symptoms via the trigeminal-autonomic reflex, or it may be an effect of different hypothalamic activity between the two syndromes, in the central disinhibition of the trigeminal-autonomic reflex by the hypothalamus (Benjamin et al., 2004), the direct hypothalamic-trigeminal connections (Malick and Burstein, 1998), or the modulatory role of the hypothalamus on the trigeminovascular nociceptive pathways (Bartsch et al., 2004). This modulation may be different between SUNCT and SUNA, which may explain the negative activation in the fMRI study in SUNA.

As regards treatments, lamotrigine was effective in 68% of SUNCT and 25% of SUNA patients who tried it, and topiramate was effective in 52% SUNCT and 0% SUNA,

although there was only one SUNA patient who took topiramate. Melatonin was moderately effective in one SUNCT patient, but had little to no effect in both SUNA patients. It is possible that these figures represent a true difference in the response to medications, such that SUNCT with its more prominent V_1 autonomic features would have a more favourable outcome. Indeed animal models (Akerman and Goadsby, 2005; Storer and Goadsby, 2004) have shown that topiramate inhibits trigeminovascular activation, as measured by dura mater and superior sagittal sinus stimulation, which is mainly innervated by V_1 (Feindel et al., 1960). It may be that SUNA, with its autonomic symptoms in V_2 and V_3 , has a more muted response to these medications.

The presence of a greater range or degree of autonomic symptoms could influence the response to medications. It is widely accepted that chronic featureless headaches such as new daily persistent headache are remarkably refractory to conventional therapies (Goadsby and Boes, 2002; Takase et al., 2004), and it could be that SUNA, being relatively featureless in terms of autonomic symptoms, is also relatively resistant to medications which are useful in SUNCT.

Both syndromes did not respond to inhaled oxygen or indomethacin, and both responded well to intravenous lidocaine. These results would indicate that SUNCT and SUNA are on the same spectrum of disorders, which are short-lasting unilateral neuralgiform headache attacks with a variable degree of cranial autonomic symptoms.

Chapter 20

Conclusions

SUNCT and SUNA are rare primary autonomic headache syndromes which have been poorly understood due to the small numbers of patients in previous studies. Their pathophysiology has been speculated to involve the posterior hypothalamus, according to some of their shared clinical characteristics with other TACs such as CH and PH, and with evidence of functional imaging studies and deep brain stimulation in the posterior hypothalamic region.

This project has undertaken a prospective clinical study in a large group of 52 SUNCT and SUNA patients. The phenotype of these two conditions has been characterised, and suggestions have been proposed to the current classifications by the International Headache Society, including: a wider variation of attack character, frequency and duration; the concept of attack load in minutes of pain per day; the ability to trigger attacks by cutaneous stimuli, and the lack of refractory period.

Clinical studies have shown that SUNCT and SUNA do not respond to inhaled oxygen or intramuscular indomethacin, in contrast with CH and PH respectively. Intravenous lidocaine, lamotrigine, topiramate and gabapentin have been shown to be useful in SUNCT and SUNA, although the shortcomings and methodological issues of double-blind placebo-controlled trials have been highlighted.

Functional imaging work has shown activation in the region of the posterior hypothalamus or in the anterior hypothalamic region in individual cases of SUNCT and SUNA. The difference between patients in terms of laterality of the activation, location of the hypothalamic region which was activated, and polarity of the activation has been discussed. A voxel-based morphometric study found no difference in structure in the hypothalamic region compared to normal controls, and this is contrasted with the findings

in CH that showed co-localisation of structural and functional changes in the posterior hypothalamus.

The differences between SUNCT and SUNA have been addressed with regard to clinical phenotypes, response to medication, and the finding of negative activation on fMRI in SUNA. It is speculated that SUNA and SUNCT have differing hypothalamic activation which may result the lack of V₁ cranial autonomic symptoms in SUNA and a reduction in cutaneous triggerability.

A fundamental tenet of primary headache syndromes is the lack of underlying structural abnormality in the brain. However TACs are known to exist as a result of other disorders, including pituitary and posterior fossa lesions. This study presents new cases of symptomatic SUNCT and SUNA, and speculates the pathophysiological differences as a result of one case of symptomatic SUNCT with no significant hypothalamic activation.

It is possible that although all TACs share some aspects of their phenotypes, and also both CH and SUNCT respond to deep brain stimulation at the posterior hypothalamus, the pathophysiology of these syndromes is different. This may be manifest by a structural change in the hypothalamus in CH, with no such change in SUNCT/SUNA, and also in the more uniform activation of the ipsilateral posterior hypothalamic region in CH and PH, as compared to activations in SUNCT and SUNA over a wider area. SUNCT and SUNA are also phenotypically different to the other TACs in that the attacks are less stereotyped within the condition, with a wide range of attack duration and frequency, and with striking features such as triggering by cutaneous stimuli and lack of a refractory period between attacks. They also have a remarkable response to intravenous lidocaine, which can aid not just in diagnosis of these conditions, but which can also afford a painfree (and therefore drug-free) respite period for up to six months after cessation of the infusion.

The hypothesis that SUNCT and SUNA are associated with activation in the posterior hypothalamic region is upheld on an individual patient basis, but more evidence is needed

that these are as strongly related to the hypothalamus as was previously thought. There is a need for biochemical evidence of hypothalamic derangement in these conditions, and from a clinical perspective a group of patients with SUNCT and SUNA should be followed up for deep brain hypothalamic stimulation in the long term. Preclinical studies to ascertain the mechanism of action of lidocaine, topiramate and lamotrigine in these particular syndromes are needed.

In the meantime, the suggestion is to widen the range of diagnostic criteria, and treat SUNCT and SUNA with intravenous lidocaine, lamotrigine, topiramate, and gabapentin especially in SUNA. Greater Occipital Nerve injections and Occipital Nerve Stimulators emerge as a new concept in treatment. Deep brain hypothalamic stimulation remains a possibility in the future, but with the reservation that the previously proposed hypothalamic activity in all TACs may not be the only mechanism for the pathophysiology of SUNCT and SUNA.

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Appendix

Appendix 1

International Headache Classification of Cluster Headache and other TACs

3.1 Cluster Headache

Diagnostic Criteria:

A: at least 5 attacks fulfilling B-D

B: severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 150-180 minutes if untreated

C: headache is accompanied by at least one of the following:

- 1) ipsilateral conjunctival injection and/or lacrimation
- 2) ipsilateral nasal congestion and/or rhinorrhoea
- 3) ipsilateral eyelid oedema
- 4) ipsilateral forehead and facial sweating
- 5) ipsilateral miosis and/or ptosis
- 6) a sense of restlessness or agitation

D: attacks have a frequency from one every other day to 8 a day

E: not attributed to another disorder

3.1.1 Episodic Cluster Headache

Diagnostic Criteria:

A: attacks fulfilling criteria A-E for 3.1 Cluster Headache

B: at least two cluster periods lasting 7-365 days and separated by pain-free remission periods of ≥ 1 month

3.1.2 Chronic Cluster Headache

Diagnostic Criteria:

A: attacks fulfilling criteria A-E for 3.1 Cluster Headache

B: attacks recur over >1 year without remission periods, or with remission periods lasting < 1 month

3.2 Paroxysmal Hemicrania

Diagnostic Criteria:

A: at least 20 attacks fulfilling B-D

B: attacks of severe unilateral orbital, supraorbital or temporal pain lasting 2-30 minutes

C: headache is accompanied by at least one of the following:

- 1) ipsilateral conjunctival injection and/or lacrimation
- 2) ipsilateral nasal congestion and/or rhinorrhoea
- 3) ipsilateral eyelid oedema
- 4) ipsilateral forehead and facial sweating
- 5) ipsilateral miosis and/or ptosis

D: attacks have a frequency of above 5 per day for more than half the time, although periods with lower frequency may occur

E: Attacks are completely prevented by therapeutic doses of indomethacin

F: not attributed to another disorder

3.3 Short lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT)

Diagnostic Criteria:

A: at least 20 attacks fulfilling B-D

B: attacks of severe unilateral orbital, supraorbital or temporal stabbing or pulsating pain lasting 5-240 seconds

C: pain is accompanied by ipsilateral conjunctival injection and lacrimation

D: attacks occur with a frequency of 3 to 200 per day

E: not attributed to another disorder

*After (Headache Classification Committee of The International Headache Society, 2004)

Headache Classification Committee of The International Headache Society.

Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain (second edition). Cephalalgia 2004; 24: 1-160.

Appendix 2

Paroxysmal Hemicrania Responding to Topiramate

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Abstract

Chronic Paroxysmal Hemicrania (CPH) is a rare primary headache syndrome which is classified along with cluster headache and SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing) as a Trigeminal Autonomic Cephalalgias (TACs). CPH is exquisitely responsive to indomethacin so much that the response is part of the current diagnostic criteria. We report a patient with CPH who had significant epigastric symptoms on indomethacin and responded well to Topiramate 150mg daily. Cessation of Topiramate caused return of attacks, and the response has persisted for two years. Topiramate may be a treatment option in CPH.

Chronic Paroxysmal Hemicrania (CPH) is a rare primary headache syndrome which is classified along with cluster headache and SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing) as a Trigeminal Autonomic Cephalalgias (TACs) (1). The International Headache Society (IHS) classification criteria (2) require relatively short-lasting (2-30 min) attacks of severe unilateral orbital, supraorbital or temporal pain accompanied by cranial autonomic symptoms. The attacks are prevented completely by therapeutic doses of indomethacin (3). The main troublesome side effect of indomethacin is gastric irritation in about one-quarter of patients (4), which has necessitated the withdrawal of indomethacin in CPH, and use of alternatives, such as cyclo-oxygenase 2 (COX-2) inhibitors, rofecoxib, valdecoxib and celecoxib (5-7), and calcium channel blockers (8).

We report a patient with CPH with a good response to indomethacin that had to be withdrawn due to gastric side effects, who had a subsequent good and prolonged response to topiramate.

Case Report

A 42 year old man sustained an injury to the left side of the face in 2001; the next day he started experiencing attacks of severe pain in the left temple, lasting 2-30 minutes (average duration 15 minutes). They were accompanied by ipsilateral conjunctival injection, lacrimation, nasal blockage, and eyelid oedema. There was no nausea, vomiting, photophobia, phonophobia or osmophobia. He would experience 15-20 attacks per day, which sometimes clustered during the day but could wake him from sleep. Movement would not make the pain worse, although he tended to keep still during an attack. There were no aura symptoms.

He had never had similar headache problems. He had some milder headaches in the past which were throbbing, beginning in the neck and radiating to the frontal region, with pain aggravated by movement lasting for some hours. There were no other features.

He had a family history of migraine in his father, who was now deceased.

There were no other medical problems. He was a non-smoker and drank no alcohol. Cranial nerve examination was normal, as was the rest of the neurological examination.

He received indomethacin 50 mg three times daily, which reduced the length of his attacks to 30-120 seconds, the frequency to 8-10 a day, and the severity from 8/10 to 5/10 on a verbal rating scale. High flow oxygen (12 litres/minute) took the edge off

the pain. Intranasal lidocaine and subcutaneous sumatriptan 6mg were not beneficial. A single dose of intramuscular indomethacin 100mg abolished his attacks for several hours (3). His clinical picture and response to indomethacin is consistent with a diagnosis of CPH based on the International Classification of Headache Disorders (2).

He was discharged from hospital on Indomethacin 50 mg tds and Ranitidine. After six weeks he developed epigastric pains, and was switched to a proton pump inhibitor. He was prescribed celecoxib instead of the indomethacin, at doses up to 400 mg daily, with inconsistent, sometimes, useful effect on his headaches.

He was then prescribed topiramate at an increasing dose starting at 25 mg daily. At doses from 200 to 350 mg daily he had almost complete abolition of his attacks, but noticed side effects of cognitive slowing, dry mouth and weight loss. At a lower dose of 100 mg daily there was a moderate effect with 3-4 attacks a day of 5-10 minutes in duration. Thereafter an intermediate dose of 150 mg daily was achieved, with only 1-2 attacks per day. At two years follow-up he still has good control of his attacks.

When he reduces the dose the attacks return.

Discussion

This patient has post-traumatic chronic paroxysmal hemicrania (CPH), which has been described previously (9). Indomethacin affected a good response, but had to be stopped due to gastric side effects. In his case a COX-2 inhibitor had no effect, although they have been reported as effective in other cases of CPH (5-7), and hemicrania continua (10). However, the recent findings that chronic high-dose COX-2 inhibitors are associated with an increased risk of ischemic heart disease and heart failure (11), plus the lack of response of some patients to COX-2 inhibitors, necessitates a suitable alternative preventive be identified. It is our experience that verapamil is not often helpful in patients with paroxysmal hemicrania in contrast to cluster headache.

Topiramate is a neuromodulator which is effective in the prevention of migraine, as shown in placebo-controlled trials (12-14), and in open-label trials in cluster headache (15-18) and SUNCT (19-22), although a robust response has not been seen in all open-label trials (23-25). There is a case report of the effectiveness of topiramate in paroxysmal hemicrania-tic syndrome (26).

Topiramate is also used in the treatment of other painful conditions, including painful diabetic neuropathy (27). It has been reported as useful in intercostal neuralgia (28), and in a case series of trigeminal neuralgia (29), but not in a placebo-controlled study (30). Topiramate has multiple mechanisms of action (31). They include modulating voltage-gated sodium ion channels, blocking excitatory glutamate receptors,

modulating voltage-gated calcium ion channels, inhibiting carbonic anhydrase, and enhancement of inhibitory GABA-mediated chloride influx through GABA_A receptors (32). Inhibition of trigeminovascular nociceptive traffic is seen with topiramate in experimental animals (33), and this action seems to reside outside the trigeminocervical complex (34). The known side effects of topiramate include somnolence, paraesthesia, diminished appetite, nausea, diarrhea, weight loss, abdominal pain and dysgeusia (35). Central nervous system adverse events included somnolence, insomnia, memory difficulty, language problems, concentration difficulty, mood problems and anxiety (35). Additionally, renal calculi and paraesthesia occur rarely (31), attributed to weak carbonic anhydrase inhibition by topiramate. It is suggested that starting at low doses, once or twice daily, and making small increments thereafter can minimize side effects; such was the case in a group of cluster headache patients (15). It is noted in our patient that the side effects were present only at higher doses (more than 200 mg/day), and he came to a suitable compromise on an intermediate dose at which there were no adverse effects, but his CPH attacks were adequately suppressed. Accepting the limitations of no placebo treatment the recrudescence of the attacks with cessation of treatment, the prolonged effect and natural history of CPH each argue for a real therapeutic effect in this case.

Given the success of topiramate in other primary headaches and pain syndromes, this report of a beneficial effect of topiramate in paroxysmal hemicrania in our patient highlights its usefulness in TACs, especially in cases where indomethacin and other preventive therapies are not viable.

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Appendix 3

Protocol For Use of Intravenous Lidocaine

Indication

Treatment of intractable headache in hospital.

Contraindications and warnings

Cardiac arrhythmias, pregnancy and lactation.

Caution: epilepsy, peptic ulceration, psychiatric disease.

Interactions: propranolol and cimetidine (reduced renal and hepatic clearance of lidocaine increases toxicity).

Dosage

Loading (optional): patients may be loaded with a dose of 1 mg/kg intravenously over 15 minutes if the clinical state indicates the need for rapid resolution of symptoms.

Infusion regime: intravenously at a dose of 1–4 mg/minute (maximum rate 3.4 mg/kg/hr).

Total treatment period: patients should not be treated for more than seven consecutive days.

Monitoring

Patients should have a resting 12-lead electrocardiogram (ECG), liver enzymes and renal function tests (hypokalaemia should be corrected) performed before administration.

Patients should have continuous cardiac monitoring. After each dose escalation, pulse rate and blood pressure should be measured every 5 minutes for first 30 minutes, then every 15 minutes for 4 hours, and thereafter four hourly.

Adverse effects

Cardiac arrhythmias and hypotension. Sensation of heat or cold, numbness, paraesthesia, nystagmus, twitching and tremor are signs of high plasma levels and treatment should be reviewed before continuation. Convulsions, cardiovascular collapse and respiratory arrest are symptoms of an overdose. Psychiatric symptoms including paranoid ideation may be triggered and the infusion should be stopped.

After (Matharu et al., 2003)

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